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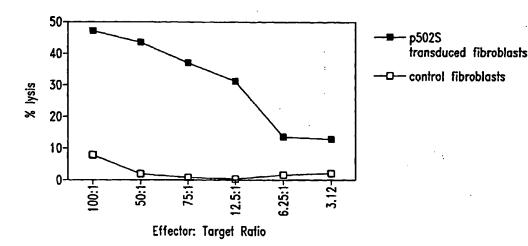
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(54) Title: COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.



1/25272 A2

# COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

#### TECHNICAL FIELD

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

#### **BACKGROUND OF THE INVENTION**

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating

such cancers. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and (c) complements of any of the sequence of (a) or (b). In certain specific embodiments, such a polypeptide comprises at least a portion, or variant thereof, of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount

detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate tumor polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate tumor polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate tumor polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate tumor antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferongamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

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- SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1
- SEO ID NO: 6 is the determined 3' cDNA sequence for H1-9
- SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4
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SEQ ID NO: 259 is the determined cDNA sequence for JP1B1 SEQ ID NO: 260 is the determined cDNA sequence for JP1B2 SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEO ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEO ID NO: 272 is the determined cDNA sequence for JP1A9 SEO ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEO ID NO: 276 is the determined cDNA sequence for JP1C11 SEO ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEO ID NO: 279 is the determined cDNA sequence for JP1A12 SEO ID NO: 280 is the determined cDNA sequence for JP8G2 SEO ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEO ID NO: 286 is the determined cDNA sequence for JP8G4 SEO ID NO: 287 is the determined cDNA sequence for JP8B6 SEO ID NO: 288 is the determined cDNA sequence for JP8D6

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SEQ ID NO: 289 is the determined cDNA sequence for JP8F5
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8
SEO ID NO: 291 is the determined cDNA sequence for JP8C7
SEQ'ID NO: 292 is the determined cDNA sequence for JP8D7
SEQ ID NO: 293 is the determined cDNA sequence for P8D8
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8
SEO ID NO: 297 is the determined cDNA sequence for JP8B10
SEO ID NO: 298 is the determined cDNA sequence for JP8C10
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9
SEQ ID NO: 302 is the determined cDNA sequence for JP8H9
SEQ ID NO: 303 is the determined cDNA sequence for JP8C12
SEQ ID NO: 304 is the determined cDNA sequence for JP8E11
SEO ID NO: 305 is the determined cDNA sequence for JP8E12
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12
SEQ ID NO: 307 is the determined cDNA sequence for P711P
SEO ID NO: 308 is the determined cDNA sequence for P712P
SEO ID NO: 309 is the determined cDNA sequence for CLONE23
SEQ ID NO: 310 is the determined cDNA sequence for P774P
SEQ ID NO: 311 is the determined cDNA sequence for P775P
SEO ID NO: 312 is the determined cDNA sequence for P715P
SEQ ID NO: 313 is the determined cDNA sequence for P710P
SEQ ID NO: 314 is the determined cDNA sequence for P767P
SEO ID NO: 315 is the determined cDNA sequence for P768P
SEQ ID NO: 316-325 are the determined cDNA sequences of previously isolated genes
SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5
SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5
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SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26

SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26

SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23

SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23

SEQ ID NO: 332 is the determined full length cDNA sequence for P509S

SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred

to as 11-C9)

SEO ID NO: 334 is the determined cDNA sequence for P714P

SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-

F3)

SEQ ID NO: 336 is the predicted amino acid sequence for P705P

SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

SEQ ID NO: 338 is the amino acid sequence of the peptide p5

SEQ ID NO: 339 is the predicted amino acid sequence of P509S

SEQ ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P

SEQ ID NO: 342 is the determined cDNA sequence for P789P

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to

Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to

Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEO ID NO: 345 is the determined cDNA sequence for a clone showing homology to

Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to

Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to

Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to

Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to

Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEO ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of

B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 375.

- SEQ ID NO: 381 is the determined cDNA sequence for B716P.
- SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.
- SEQ ID NO: 383 is the predicted amino acid sequence for P711P.
- SEQ ID NO: 384 is the cDNA sequence for P1000C.
- SEQ ID NO: 385 is the cDNA sequence for CGI-82.
- SEQ ID NO:386 is the cDNA sequence for 23320.
- SEQ ID NO:387 is the cDNA sequence for CGI-69.
- SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.
- SEQ ID NO:389 is the cDNA sequence for 23379.
- SEQ ID NO:390 is the cDNA sequence for 23381.
- SEQ ID NO:391 is the cDNA sequence for KIAA0122.
- SEQ ID NO:392 is the cDNA sequence for 23399.
- SEO ID NO:393 is the cDNA sequence for a previously identified gene.
- SEQ ID NO:394 is the cDNA sequence for HCLBP.
- SEQ ID NO:395 is the cDNA sequence for transglutaminase.
- SEQ ID NO:396 is the cDNA sequence for a previously identified gene.
- SEQ ID NO:397 is the cDNA sequence for PAP.
- SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.
- SEQ ID NO:399 is the cDNA sequence for hTGR.
- SEQ ID NO:400 is the cDNA sequence for KIAA0295.
- SEQ ID NO:401 is the cDNA sequence for 22545.
- SEQ ID NO:402 is the cDNA sequence for 22547.
- SEQ ID NO:403 is the cDNA sequence for 22548.
- SEQ ID NO:404 is the cDNA sequence for 22550.
- SEQ ID NO:405 is the cDNA sequence for 22551.
- SEQ ID NO:406 is the cDNA sequence for 22552.
- SEQ ID NO:407 is the cDNA sequence for 22553.
- SEQ ID NO:408 is the cDNA sequence for 22558.
- SEQ ID NO:409 is the cDNA sequence for 22562.
- SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567. SEQ ID NO:412 is the cDNA sequence for 22568. SEQ ID NO:413 is the cDNA sequence for 22570. SEQ ID NO:414 is the cDNA sequence for 22571. SEQ ID NO:415 is the cDNA sequence for 22572. SEO ID NO:416 is the cDNA sequence for 22573. SEQ ID NO:417 is the cDNA sequence for 22573. SEQ ID NO:418 is the cDNA sequence for 22575. SEQ ID NO:419 is the cDNA sequence for 22580. SEQ ID NO:420 is the cDNA sequence for 22581. SEO ID NO:421 is the cDNA sequence for 22582. SEQ ID NO:422 is the cDNA sequence for 22583. SEQ ID NO:423 is the cDNA sequence for 22584. SEQ ID NO:424 is the cDNA sequence for 22585. SEO ID NO:425 is the cDNA sequence for 22586. SEQ ID NO:426 is the cDNA sequence for 22587. SEQ ID NO:427 is the cDNA sequence for 22588. SEQ ID NO:428 is the cDNA sequence for 22589. SEQ ID NO:429 is the cDNA sequence for 22590. SEQ ID NO:430 is the cDNA sequence for 22591. SEQ ID NO:431 is the cDNA sequence for 22592. SEQ ID NO:432 is the cDNA sequence for 22593. SEQ ID NO:433 is the cDNA sequence for 22594. SEQ ID NO:434 is the cDNA sequence for 22595. SEQ ID NO:435 is the cDNA sequence for 22596. SEO ID NO:436 is the cDNA sequence for 22847. SEQ ID NO:437 is the cDNA sequence for 22848. SEQ ID NO:438 is the cDNA sequence for 22849. SEQ ID NO:439 is the cDNA sequence for 22851. SEQ ID NO:440 is the cDNA sequence for 22852.

- SEQ ID NO:441 is the cDNA sequence for 22853.
- SEQ ID NO:442 is the cDNA sequence for 22854.
- SEQ ID NO:443 is the cDNA sequence for 22855.
- SEQ ID NO:444 is the cDNA sequence for 22856.
- SEQ ID NO:445 is the cDNA sequence for 22857.
- SEQ ID NO:446 is the cDNA sequence for 23601.
- SEQ ID NO:447 is the cDNA sequence for 23602.
- SEQ ID NO:448 is the cDNA sequence for 23605.
- SEQ ID NO:449 is the cDNA sequence for 23606.
- SEQ ID NO:450 is the cDNA sequence for 23612.
- SEQ ID NO:451 is the cDNA sequence for 23614.
- SEQ ID NO:452 is the cDNA sequence for 23618.
- SEQ ID NO:453 is the cDNA sequence for 23622.
- SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
- SEQ ID NO:455 is the cDNA sequence for LIM protein.
- SEQ ID NO:456 is the cDNA sequence for a known gene.
- SEO ID NO:457 is the cDNA sequence for a known gene.
- SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
- SEQ ID NO:459 is the cDNA sequence for 23045.
- SEQ ID NO:460 is the cDNA sequence for 23032.
- SEQ ID NO:461 is the cDNA sequence for 23054.
- SEQ ID NOs:462-467 are cDNA sequences for known genes.
- SEQ ID NOs:468-471 are cDNA sequences for P710P.
- SEQ ID NO:472 is a cDNA sequence for P1001C.
- SEQ ID NO:473 is the amino acid sequence for PSMA.
- SEQ ID NO:474 is the amino acid sequence for PAP.
- SEQ ID NO:475 is the amino acid sequence for PSA.
- SEQ ID NO:476 is the amino acid sequence for a fusion protein containing PSA, P703P and P501S.

#### DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer. The compositions described herein may include prostate tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a prostate tumor protein or a variant thereof. A "prostate tumor protein" is a protein that is expressed in prostate tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain prostate tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a Antibodies are generally immune system proteins, or antigen-binding sequence. fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human prostate tumor proteins. Sequences of polynucleotides encoding certain tumor proteins, or portions thereof, are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Sequences of polypeptides comprising at least a portion of a tumor protein are provided in SEQ ID NOs:112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

#### PROSTATE TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a prostate tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a prostate tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a prostate tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a prostate tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native prostate tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions,

usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are

capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native prostate tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a prostate tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding at least a portion of a prostate tumor protein are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Isolation of these polynucleotides is described below. Each of these prostate tumor proteins was overexpressed in prostate tumor tissue.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may

also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a prostate tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a prostate tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

#### PROSTATE TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a prostate tumor protein or a variant thereof, as described herein. As noted above, a "prostate tumor protein" is a protein that is expressed by prostate tumor cells. Proteins that are prostate tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera

and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigenspecific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most

preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. Α "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression

vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be

targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

In certain embodiments, the present invention provides fusion proteins comprising a polypeptide disclosed herein together with at least one of the following known prostate antigens: prostate specific antigen (PSA); prostatic acid phosphatase (PAP); and prostate specific membrane antigen (PSMA). The protein sequences for PSMA, PAP and PSA are provided in SEQ ID NO: 473-475, respectively. In certain embodiments, the fusion proteins of the present invention comprise PSA, PAP and/or PSMA in combination with one or more of the following the inventive antigens: P501S (amino acid sequence provided in SEQ ID NO: 113); P703P (amino acid sequences provided in SEQ ID NO: 327, 329, 331); P704P (cDNA sequence provided in SEQ ID NO: 67); P712P (cDNA sequence provided in SEQ ID NO: 308); P775P (cDNA sequence provided in SEQ ID NO: 311); P776P (cDNA sequence provided in SEQ ID NO: 354); P790P (cDNA sequence provided in SEQ ID NO: 352). The amino acid sequence of a fusion protein of PSA, P703P and P501S is provided in SEQ ID NO: 476. In preferred embodiments, the inventive fusion proteins comprise one of the following combinations of antigens: PSA and P703P; PSA and P501S; PAP and P703P; PAP and P501S; PSMA and P703P; PSMA and P501S; PSA, PAP and P703P; PSA, PAP and P501S; PSA, PAP, PSMA and P703P, PSA, PAP, PSMA and P501S. One of skill in the art will appreciate that the order of polypeptides within a fusion protein can be altered without substantially changing the therapeutic, prophylactic or diagnostic properties of the fusion protein.

The fusion proteins described above are more immunogenic and will be effective in a greater number of prostate cancer patients than any of the individual components alone. The use of multiple antigens in the form of a fusion protein also lessens the likelihood of immunologic escape.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide

components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-

terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

#### **BINDING AGENTS**

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal

indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested

by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

#### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (*see also* U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate tumor polypeptide, polynucleotide encoding a prostate tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively,

detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4+ and/or CD8<sup>+</sup>. Prostate tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

#### PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions

or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner

et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be

formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically microspheres: polysaccharides; polyphosphazenes; biodegradable derivatized monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt.

MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific

immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see Zitvogel et al.*, *Nature Med. 4:*594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into

dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a prostate tumor protein (or portion or other variant thereof) such that the prostate tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be

pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

#### **CANCER THERAPY**

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth in vitro, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccinedependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-In general, for pharmaceutical compositions and vaccines vaccinated patients. comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from

the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween  $20^{\text{TM}}$ . The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a prostate tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with prostate tumor polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8+ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a prostate tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%,

preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375 and 381. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter

performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate tumor protein in a biological sample. Such kits generally comprise

at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

#### **EXAMPLES**

#### **EXAMPLE 1**

# ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the Notl/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/Notl site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained 1.64 x 10<sup>7</sup> independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained 3.3 x 10<sup>6</sup> independent colonies, with 69% of clones

having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 μg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μl of H<sub>2</sub>O, heat-denatured and mixed with 100 μl (100 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax E.

coli DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12. This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the

driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to nonhuman sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193,

respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be overexpressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEO ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339.

#### **EXAMPLE 2**

## DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate tumor polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with genespecific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed at lower levels in all other tissues tested.

expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis et al. (Proc. Natl. Acad. Sci. USA 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive

cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

### **EXAMPLE 3**

## ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to

previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor

compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor

and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX 23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively.

The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted

amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

### EXAMPLE 4 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

#### **EXAMPLE 5**

### FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were

separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig

valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be

expressed in small intestine. Of the 26 clones, 10 (SEQ ID NO: 340-349) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350-365.

### **EXAMPLE 6**

### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2.1 (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-Ab binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells (5 x 105/ml) were restimulated with 2.5 x 106/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, Science 258:815-818, 1992) and 3 x 106/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells

as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2.1 expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2.1 molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2.1 were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg

of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

# EXAMPLE 7 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE TUMOR POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed in vitro to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (Critical Reviews in Immunology 18:65-75, 1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a y-interferon ELISPOT assay (see Lalvani et al., J. Exp. Med. 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on  $10^4$  fibroblasts in the presence of 3 µg/ml human  $\beta_2$ microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a y-interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of y-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of  $\gamma$ interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

### **EXAMPLE 8**

### PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate tumor antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg VR10132-P501S either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed A2-restricted CTL epitope.

#### **EXAMPLE 9**

## GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE TUMOR ANTIGEN

Using *in vitro* whole-gene priming with P501S-retrovirally transduced autologous fibroblasts (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched fibroblast lines transduced with P501S, these CTL lines were shown to be restricted HLA-A2 class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured

overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S-transduced autologous fibroblasts. The P501S-specific activity could be sustained by the continued stimulation of the cultures with P501S-transduced fibroblasts in the presence of IL-15. A panel of HLA-mismatched fibroblast lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be restricted by HLA-A2. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

#### **EXAMPLE 10**

## IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE TUMOR ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2 transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of P703P transduced target cells expressing either HLA-A2Kb or HLA-A2. Specifically, HLA-A2 transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* 

stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with p5 peptide and cultured with GM-CSF and IL-4 together with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated.

### **EXAMPLE 11**

## EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate tumor and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach).

#### **EXAMPLE 12**

### ELICITATION OF PROSTATE TUMOR ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate tumor antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8+ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501Stransduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxity assays (51Cr release) and interferon-gamma production (Interferon-gamma Elispot; see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

# EXAMPLE 13 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA ,	P510S	
Ald. 6 Dehyd.	P784P .	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang(23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	·
HDLBP (23508; SEQ ID NO:394)	·	
CG1-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG .		

CGI-82 showed 4.06 fold over-expression in prostate tissues as

compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal The expression of this gene in normal tissues was very low. prostate tissues. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of

normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

# EXAMPLE 14 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate tumor antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped

(aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups, Plus (normal prostate and prostate tumor libraries, and breast cell lines, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

<u>Table II</u>
Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones found in the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones found in the Plus, Minus and Other group libraries, but the

expression in the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones found in Plus, Minus and Other group libraries, but the expression in the Plus group is higher than the expression in the Minus group. This analysis identified 4,345 breast clusters (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

<u>Table III</u>

Prostate Cluster Summary

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (i.e., the level in prostate tumor cDNA was at least three times the level in normal prostate cDNA) were

identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NOs:401-453, with certain novel sequences shown in SEQ ID NOs:407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u>

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments	
401	22545	previously identified P1000C	
402	22547	previously identified P704P	
403	22548	known	
404	22550	known	
405	22551	PSA	
406	22552	prostate secretory protein 94	
407	22553	novel	
408	22558	previously identified P509S	
409	22562	glandular kallikrein	
410	22565	previously identified P1000C	
411	22567	PAP	
412	22568	B1006C (breast tumor antigen)	
413	22570	novel	
414	22571	PSA	
415	22572	previously identified P706P	
416	22573	novel	
417	22574	novel	
418	22575	novel	
419	22580	novel	
420	22581	PAP	
421	22582	prostatic secretory protein 94	
422	22583	novel	
423	22584	prostatic secretory protein 94	
424	22585	prostatic secretory protein 94	
425	22586	known	
426	22587	novel	
427	22588	novel	
428	22589	PAP	
429	22590	known	
430	22591	PSA	
431	22592	known	
432	22593	Previously identified P777P	

433	22594	T cell receptor gamma chain	
434	22595	Previously identified P705P	
435	22596	Previously identified P707P	
436	22847	PAP	
437	22848	known	
438	22849	prostatic secretory protein 57	
439	22851	PAP	
440	22852	PAP	
441	22853	PAP	
442	22854	previously identified P509S	
443	22855	previously identified P705P	
444	22856	previously identified P774P	
445	22857	PSA	
446	23601	previously identified P777P	
447	23602	PSA	
448	23605	PSA	
449	23606	PSA	
450	23612	novel	
451	23614	PSA	
452	23618	previously identified P1000C	
453	23622	previously identified P705P	

# EXAMPLE 15 FURTHER IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NOs:454-467. Of these sequences SEQ ID NOs:459-461 correspond to novel genes. The others (SEQ ID NOs:454-458 and 461-467) correspond to known sequences.

### **EXAMPLE 16**

### FURTHER CHARACTERIZATION OF PROSTATE TUMOR ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic ABI Sequencer. Four sequences were obtained, and are presented in SEQ ID NOs:468-471.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

### CLAIMS

- 1. An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472;
- (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and
  - (c) complements of any of the sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 339 and 383.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate tumor protein, or a variant thereof that differs in one or more

substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.

- 5. An isolated polynucleotide encoding a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 7. An isolated polynucleotide comprising a sequence that hybridizes, under moderately stringent conditions, to a sequence recited in any one of

SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.

- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims 4-7.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An expression vector comprising a polynucleotide according claim 8.
- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- 13. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
- 14. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 15. A vaccine according to claim 14, wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine according to claim 14, wherein the non-specific immune response enhancer induces a predominantly Type I response.

- 17. A pharmaceutical composition comprising a polynucleotide according to claim 4, in combination with a physiologically acceptable carrier.
- 18. A vaccine comprising a polynucleotide according to claim 4, in combination with a non-specific immune response enhancer.
- 19. A vaccine according to claim 18, wherein the non-specific immune response enhancer is an adjuvant.
- 20. A vaccine according to claim 18, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 21. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472 or a complement of any of the foregoing polynucleotide sequences.
- 22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 26. A vaccine according to claim 25, wherein the non-specific immune response enhancer is an adjuvant.
- 27. A vaccine according to claim 25, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-

binding fragment thereof according to claim 21, and thereby inhibiting the development of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is prostate cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.

40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.

- 41. A vaccine comprising a fusion protein according to claim 35, in combination with a non-specific immune response enhancer.
- 42. A vaccine according to claim 41, wherein the non-specific immune response enhancer is an adjuvant.
- 43. A vaccine according to claim 41, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with a non-specific immune response enhancer.
- 46. A vaccine according to claim 45, wherein the non-specific immune response enhancer is an adjuvant.
- 47. A vaccine according to claim 45, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.

49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.

- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
- (ii) complements of the foregoing polynucleotides;
  wherein the step of contacting is performed under conditions and for a
  time sufficient to permit the removal of cells expressing the prostate tumor protein from
  the sample.
- 51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.
- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and/or

(iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.
- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

- (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate;

- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

59. A method according to claim 58, wherein the binding agent is an antibody.

- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.
- 61. A method according to claim 58, wherein the cancer is prostate cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.

65. A method according to claim 62, wherein the cancer is a prostate cancer.

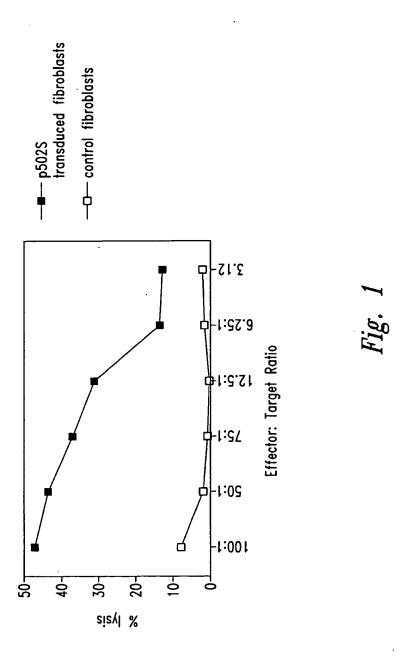
- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor

protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;

- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 72. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 21; and
  - (b) a detection reagent comprising a reporter group.
- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.

75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotides.
- 78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
  - 79. A diagnostic kit, comprising:
  - (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.



2/6

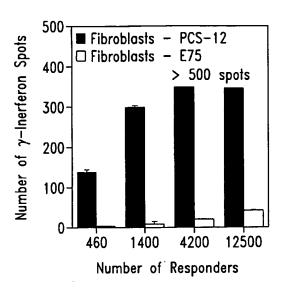


Fig. 2A

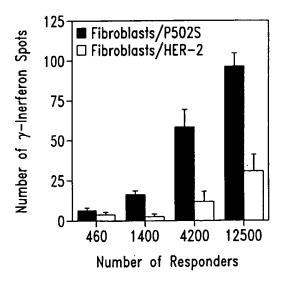
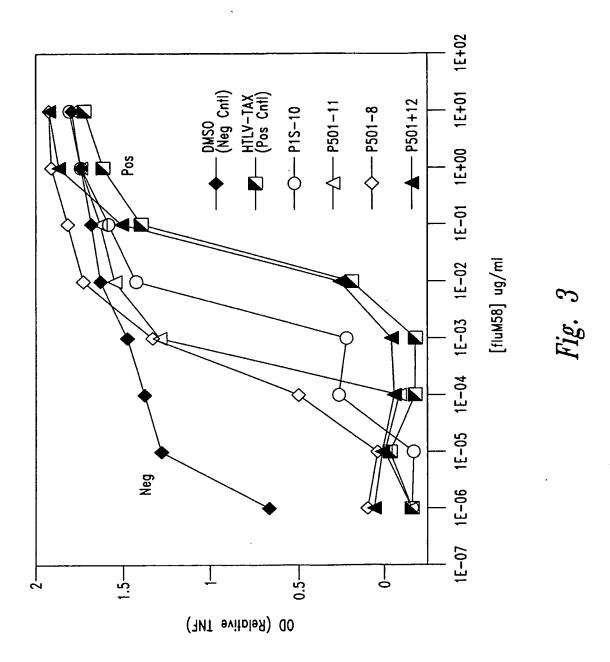
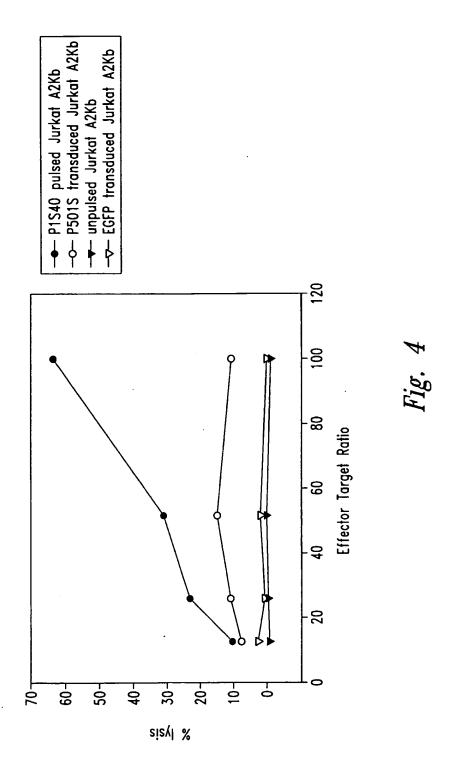
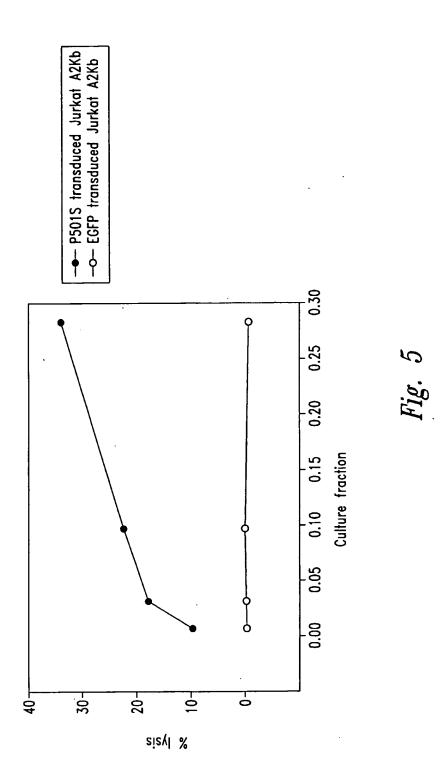


Fig. 2B







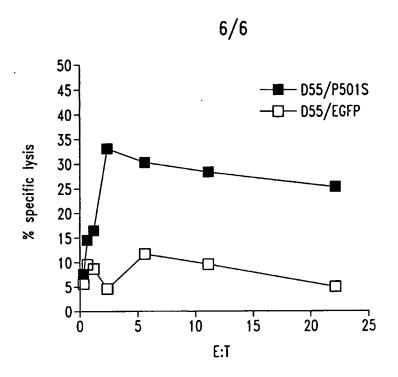


Fig. 6A

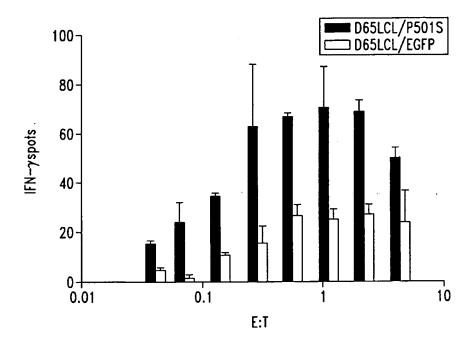


Fig. 6B

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        <221> misc_feature
        <222> (1)...(814)
        <223> n = A, T, C or G
ttttttttt tttttcacag tataacagct ctttatttct gtgagttcta ctaggaaatc
                                                                                           60
                                                                                          120
atcaaatctg agggttgtct ggaggacttc aatacacctc cccccatagt gaatcagctt
ccagggggtc cagtccctct ccttacttca tccccatccc atgccaaagg aagaccctcc
                                                                                          180
ctccttggct cacagccttc tctaggcttc ccagtgcctc caggacagag tgggttatgt
                                                                                          240
tttcagctcc atcettgctg tgagtgtctg gtgcgttgtg cctccagctt ctgctcagtg cttcatggac agtgtccagc acatgtcact ctccactctc tcagtgtgga tccactagtt
                                                                                          300 -
                                                                                          360
ctagagcggc cgccaccgcg gtggagctcc agcttttgtt ccctttagtg agggttaatt
                                                                                          420
gcgcgcttgg cgtaatcatg gtcataactg tttcctgtgt gaaattgtta tccgctcaca attccacaca acatacgagc cggaagcata aagtgtaaag cctggggtgc ctaatgagtg anctaactca cattaattgc gttgcgctca ctgnccgctt tccagtcngg aaaactgtcg
                                                                                          480
                                                                                          540
                                                                                          600
tgccagctgc attaatgaat cggccaacgc ncggggaaaa gcggtttgcg ttttgggggc
                                                                                          660
tetteegett etegeteact nanteetgeg eteggtentt eggetgeggg gaacggtate
                                                                                          720
                                                                                          780
actecteaaa ggnggtatta eggttateen naaatenggg gataeeengg aaaaaanttt
aacaaaaggg cancaaaggg cngaaacgta aaaa
                                                                                          814
        <210> 2
        <211> 816
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1) ... (816)
        <223> n = A, T, C or G
acagaaatgt tggatggtgg agcacctttc tatacgactt acaggacagc agatggggaa
                                                                                           60
ttcatggctg ttggagcaat agaaccccag ttctacgagc tgctgatcaa aggacttgga
                                                                                          120
                                                                                          180
ctaaagtctg atgaacttcc caatcagatg agcatggatg attggccaga aatgaagaag
aagtttgcag atgtatttgc aaagaagacg aaggcagagt ggtgtcaaat ctttgacggc acagatgcct gtgtgactcc ggttctgact tttgaggagg ttgttcatca tgatcacaac aaggaacggg gctcgtttat caccagtgag gagcaggacg tgagcccccg ccctgcacct ctgctgttaa acaccccagc catcccttct ttcaaaaggg atccactagt tctagaagcg
                                                                                          240
                                                                                          300
                                                                                          360
                                                                                          420
gccgccaccg cggtggagct ccagcttttg ttccctttag tgagggttaa ttgcgcgctt
                                                                                          480
```

```
540
ggcgtaatca tggtcatagc tgtttcctgt gtgaaattgt tatccgctca caattccccc
aacatacgag coggaacata aagtgttaag cotggggtgo otaatgantg agotaacton
                                                                              600
cattaattgc gttgcgctca ctgcccgctt tccagtcggg aaaactgtcg tgccactgcn
                                                                             660
ttantgaatc ngccacccc cgggaaaagg cggttgentt ttgggcctct tccgctttcc
                                                                             720
tegeteattg atcetngene eeggtetteg getgeggnga aeggtteact ceteaaagge
                                                                             780
ggtntnccgg ttatccccaa acnggggata cccnga
                                                                             816
       <210> 3
<211> 773
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (773)
       <223> n = A, T, C or G
       <400> 3
cttttgaaag aagggatggc tgggggtgttt aacagcagag gtgcagggcg ggggctcacg
                                                                              60
tcctgctcct cactggtgat aaacgagccc cgttccttgt tgtgatcatg atgaacaacc
                                                                             120
tcctcaaaag tcagaaccgg agtcacacag gcatctgtgc cgtcaaagat ttgacaccac tctgccttcg tcttctttgc aaatacatct gcaaacttct tcttcatttc tggccaatca
                                                                             180
                                                                             240
tocatgetea tetgattggg aagtteatea gaetttagte cannteettt gateageage
                                                                             300
tegtagaact ggggttetat tgeteeaaca gecatgaatt ceceatetge tgteetgtaa
                                                                             360
gtcgtataga aaggtgctcc accatccaac atgttctgtc ctcgaggggg ggcccggtac
                                                                             420
ccaattcgcc ctatantgag tcgtattacg cgcgctcact ggccgtcgtt ttacaacgtc gtgactggga aaaccctggg cgttaccaac ttaatcgcct tgcagcacat ccccctttcg
                                                                             480
                                                                             540
ccagctgggc gtaatancga aaaggcccgc accgatcgcc cttccaacag ttgcgcacct
                                                                             600
gaatgggnaa atgggaccc cctgttaccg cgcattnaac ccccgcnggg tttngttgtt
                                                                             660
acceccaent nnacegetta caetttgeca gegeettane gecegeteee ttteneettt
                                                                             720
cttcccttcc tttcncnccn ctttcccccg gggtttcccc cntcaaaccc cna
                                                                             773
      <210> 4
      <211> 828
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (828)
      <223> n = A, T, C or G
cctcctgagt cctactgacc tgtgctttct ggtgtggagt ccagggctgc taggaaaagg
                                                                              60
aatgggcaga cacaggtgta tgccaatgtt tctgaaatgg gtataatttc gtcctctct
                                                                             120
teggaacact ggetgtetet qaaqaettet eqeteaqttt caqtqaqqae acacacaaaq
                                                                             180
acgtgggtga ccatgttgtt tgtggggtgc agagatggga ggggtggggc ccaccctgga
                                                                             240
agagtggaca gtgacacaag gtggacactc tctacagatc actgaggata agctggagcc acaatgcatg aggcacacac acagcaagga tgacnctgta aacatagccc acgctgtcct
                                                                             300
                                                                             360
gngggcactg ggaagcctan atnaggccgt gagcanaaag aaggggagga tccactagtt
                                                                             420
ctanagogge egecacegeg gtgganetee anettttgtt eeetttagtg agggttaatt
                                                                             480
gcgcgcttgg cntaatcatg gtcatanctn tttcctgtgt gaaattgtta tccgctcaca
                                                                             540
attecacaca acatacgane eggaaacata aantgtaaac etggggtgee taatgantga
                                                                             600
ctaactcaca ttaattgcgt tgcgctcact gcccgctttc caatcnggaa acctgtcttg
                                                                             660
concttgcat tnatgaatch gccaaccccc ggggaaaagc gtttgcgttt tgggcgctct
                                                                             720
tecgetteet eneteantta ntecetnene teggteatte eggetgenge aaaceggtte
                                                                             780
accncctcca aagggggtat tccggtttcc ccnaatccgg gganancc
                                                                             828
      <210> 5
      <211> 834
      <212> DNA
      <213> Homo sapien
```

PCT/US00/27464 WO 01/25272

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<220>
       <221> misc_feature
       <222> (1) ... (834)
       <223> n = A,T,C or G
       <400> 5
ttttttttt tttttactga tagatggaat ttattaagct tttcacatgt gatagcacat
                                                                              60
                                                                             120
agttttaatt gcatccaaaq tactaacaaa aactctagca atcaagaatg gcagcatgtt
attttataac aatcaacacc tgtggctttt aaaatttggt tttcataaga taatttatac
                                                                             180
tgaagtaaat ctagccatgc ttttaaaaaa tgctttaggt cactccaagc ttggcagtta
                                                                             240
acatttggca taaacaataa taaaacaatc acaatttaat aaataacaaa tacaacattg
                                                                             300
                                                                             360
taggccataa tcatatacag tataaggaaa aggtggtagt gttgagtaag cagttattag
aatagaatac cttggcctct atgcaaatat gtctagacac tttgattcac tcagccctga cattcagttt tcaaagtagg agacaggttc tacagtatca ttttacagtt tccaacacat
                                                                             420
                                                                             480
tgaaaacaag tagaaaatga tgagttgatt tttattaatg cattacatcc tcaagagtta
                                                                             540
tcaccaaccc ctcagttata aaaaattttc aagttatatt agtcatataa cttggtgc
                                                                             600
ttattttaaa ttagtgctaa atggattaag tgaagacaac aatggtcccc taatgtgatt gatattggtc atttttacca gcttctaaat ctnaactttc aggcttttga actggaacat
                                                                             660
                                                                             720
tgnatnacaq tqttccanaq ttncaaccta ctgqaacatt acagtqtqct tqattcaaaa
                                                                             780
tgttattttg ttaaaaatta aattttaacc tggtggaaaa ataatttgaa atna
                                                                             834
       <210> 6
       <211> 818
       <212> DNA
       <213> Homo sapien
       <221> misc feature
       <222> (1) ... (818)
       <223> n = A, T, C or G
      <400> 6
ttttttttt tttttttt aagaccctca tcaatagatg gagacataca gaaatagtca
                                                                              60
                                                                             120
aaccacatct acaaaatgcc agtatcaggc ggcggcttcg aagccaaagt gatgtttgga
tgtaaagtga aatattagtt ggcggatgaa gcagatagtg aggaaagttg agccaataat
                                                                             180
qacqtqaaqt ccqtqqaaqc ctqtqqctac aaaaaatqtt qaqccqtaqa tqccqtcqqa
                                                                             240
                                                                             300
aatggtgaag ggagactcga agtactctga ggcttgtagg agggtaaaat agagacccag
taaaattgta ataagcagtg cttgaattat ttggtttcgg ttgtttcta ttagactatg
                                                                             360
qtqaqctcaq qtqattqata ctcctqatqc qaqtaatacq qatqtqttta qqaqtqgqac
                                                                             420
ttctagggga tttagcgggg tgatgcctgt tgggggccag tgccctccta gttggggggt
                                                                             480
aggggctagg ctggagtggt aaaaggctca gaaaaatcct gcgaagaaaa aaacttctga ggtaataaat aggattatcc cgtatcgaag gcctttttgg acaggtggtg tgtggtggcc
                                                                             540
                                                                             600
ttggtatgtg ctttctcgtg ttacatcgcg ccatcattgg tatatggtta gtgtgttggg
                                                                             660
ttantanggc ctantatgaa gaacttttgg antggaatta aatcaatngc ttggccggaa
                                                                             720
gtcattanga nggctnaaaa ggccctgtta ngggtctggg ctnggtttta cccnacccat
                                                                             780
ggaatnence ecceggaena ntgnatecet attettaa
                                                                             818
      <210> 7
      <211> 817
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (817)
      <223> n = A, T, C or G
      <400> 7
tttttttttt tttttttt tggctctaga gggggtagag ggggtgctat agggtaaata
                                                                              60
cgggccctat ttcaaagatt tttaggggaa ttaattctag gacgatgggt atgaaactgt
                                                                             120
qqtttgctcc acagatttca gagcattgac cqtagtatac ccccqqtcqt qtagcggtga
                                                                             180
```

```
240
aaqtqqtttg qtttagacgt ccgggaattg catctgtttt taagcctaat gtggggacag
ctcatgagtg caagacgtct tgtgatgtaa ttattatacn aatgggggct tcaatcggga
                                                                               300
gtactactcg attgtcaacg tcaaggagtc gcaggtcgcc tggttctagg aataatgggg
                                                                               360
gaagtatgta ggaattgaag attaatccgc cgtagtcggt gttctcctag gttcaatacc
                                                                               420
attggtggcc aattgatttg atggtaaggg gagggatcgt tgaactcgtc tgttatgtaa
                                                                               480
aggatneett ngggatggga aggenatnaa ggaetangga tnaatggegg geangatatt
                                                                               540
                                                                               600
tcaaacngtc tctanttcct gaaacgtctg aaatgttaat aanaattaan tttngttatt
gaatnttnng gaaaagggct tacaggacta gaaaccaaat angaaaanta atnntaangg
                                                                               660
cnttatentn aaaggtnata accnetecta tnateceaee caatngnatt ecceaenenn
                                                                               720
acnattggat necesantte canaaangge enceeeegg tgnanneene ettttgttee
                                                                               780
cttnantgan ggttattcnc ccctngcntt atcancc
                                                                               817
       <210> 8
       <211> 799
<212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(799)
       <223> n = A, T, C or G
       <400> 8
catttccggg tttactttct aaggaaagcc gagcggaagc tgctaacgtg ggaatcggtg
                                                                                60
                                                                               120
cataaggaga actttctgct ggcacgcgct agggacaagc gggagagcga ctccgagcgt
ctgaagcgca cgtcccagaa ggtggacttg gcactgaaac agctgggaca catccgcgag
                                                                               180
tacgaacage geetgaaagt getggagegg gaggteeage agtgtageeg egteetgggg tgggtggeeg angeetgane egetetgeet tgetgeecee angtgggeeg ecaceceetg
                                                                               240
                                                                               300
acctgcctgg gtccaaacac tgagccctgc tggcggactt caagganaac ccccacangg
                                                                               360
                                                                               420
ggattttgct cctanantaa ggctcatctg ggcctcggcc cccccacctg gttggccttg
tetttgangt gagececatg tecatetggg ceaetgteng gaceacettt ngggagtgtt eteettacaa ecacannatg eeeggeteet eeeggaaace anteceance tgngaaggat
                                                                               480
                                                                               540
caagneetgn atecaetnnt netanaaceg geeneenceg engtggaace encettntgt
                                                                               600
teetttent tnagggttaa tnnegeettg geettneean ngteetnene ntttteennt
                                                                               660
gttnaaattg ttangeneee neennteeen ennennenan eeegaeeenn annttnnann
                                                                               720
ncctgggggt nccnncngat tgacconnce nccctntant tgcnttnggg nncnntgccc
                                                                               780
                                                                               799
ctttccctct nggganncg
       <210> 9
       <211> 801
       <212> DNA
       <213> Homo sapien
      <220>
       <221> misc feature
       <222> (1)...(801)
       <223> n = A, T, C or G
      <400> 9
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                                                                                60
taangatgac acteecaaag gtggteetga cagtggeeca gatggacatg gggeteaeet
                                                                               120
                                                                               180
caaggacaag gccaccaggt gcgggggccg aagcccacat gatccttact ctatgagcaa
aatcccctgt gggggcttct ccttgaagtc cgccancagg gctcagtctt tggacccang
                                                                               240
caggicatgg ggitgingne caactggggg ceneaacgca aaanggenea gggeetengn cacceatece angaegegge tacactnetg gacetecene tecaceaett teatgegetg tientaceeg egnatnigte ceancigtit engigeenae tecanettet nggaegigeg
                                                                               300
                                                                               360
                                                                               420
ctacatacgc ccqqantcnc nctcccqctt tqtccctatc cacqtnccan caacaaattt
                                                                               480
                                                                               540
encentantg cacenattee caentttnne agnttteene nnegngette ettntaaaag
                                                                               600
ggttganccc cggaaaatnc cccaaagggg gggggccngg tacccaactn cccctnata
getgaantee ceatnacenn gnetenatgg ancenteent tttaannaen ttetnaactt
                                                                               660
gggaanance etegneentn ceccenttaa teceneettg enangnnent ecccenntee
                                                                               720
                                                                               780
ncconniting gentintiann chaaaaagge commancaa tetectinen ceteantteg
```

```
801
 ccancecteg aaateggeen e
        <210> 10
        <211> 789
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1) ... (789)
        <223> n = A, T, C or G
        <400> 10
                                                                              60
 cagtetaint ggccagtgtg gcagetttee etgtggetge eggtgeeaca tgeetgteee
                                                                             120
 acagtgtggc cgtggtgaca gcttcagccg ccctcaccgg gttcaccttc tcagccctgc
 agatectqcc ctacacactg qcctccctct accaccggga gaagcaggtg ttcctgccca
                                                                             180
 aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc
                                                                             240
                                                                             300
 caggeetaa geetggaget eeetteeta atggacaegt gggtgetgga ggeagtggee
                                                                             360
 tgctcccacc tccacccgcg ctctgcgggg cctctgcctg tgatgtctcc gtacgtgtgg
 tggtgggtga gcccaccgan gccagggtgg ttccgggccg gggcatctgc ctggacctcg
                                                                             420
 ccatcetgga tagtgettee tgetgteeca ngtggeecca tecetgtta tgggetecat tgtecagete agecagtetg teactgeeta tatggtgtet geegeaggee tgggtetggt
                                                                             480
                                                                             540
                                                                             600
 cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcagcg
 ttaaaaaatt ccagcaacat tgggggtgga aggcctgcct cactgggtcc aactccccgc
                                                                             660
                                                                             720
 tcctgttaac cccatggggc tgccggcttg gccgccaatt tctgttgctg ccaaantnat
 gtggctctct gctgccacct gttgctggct gaagtgcnta engeneanct nggggggtng
                                                                             780
                                                                             789
ggngttccc
        <210> 11
        <211> 772
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc feature
        <222> (1)...(772)
        <223> n = A, T, C or G
        <400> 11
                                                                              60
 cccaccctac ccaaatatta gacaccaaca cagaaaagct agcaatggat tcccttctac
                                                                             120
 tttgttaaat aaataagtta aatatttaaa tgcctgtgtc tctgtgatgg caacagaagg
 accaacaggc cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc
                                                                             180
 tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata actttcatat gttcaaatcc catggaggag tgtttcatcc tagaaactcc catgcaagag
                                                                             240
                                                                             300
 ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt
                                                                             360
 tattcagctc ccaaaaaccc ttctctaggt gtgtctcaac taggaggcta gctgttaacc
                                                                             420
                                                                             480
 ctgagcctgg gtaatccacc tgcagagtcc ccgcattcca gtgcatggaa cccttctggc
 ctccctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana
                                                                             540
 aactqqqqaa aaaaqaaaaq qacqccccan cccccaqctg tgcanctacg cacctcaaca
                                                                             600
 gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaaact ngggggggca
                                                                             660
 accocggcac cccnangggg gttaacagga ancngggnaa cntggaaccc aattnaggca
                                                                             720
                                                                             772
 ggcccnccac cccnaatntt gctgggaaat ttttcctccc ctaaattntt tc
        <210> 12
        <211> 751
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc feature
        <222> (1) ... (751)
        <223> n = A, T, C or G
```

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<400> 12
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                          60
agetgattga ageaaccete tactttttgg tegtgageet tttgettggt geaggtttea
                                                                         120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                         180
aagtanggtg agteetcaaa ateegtatag ttggtgaage cacageactt gageeettte
                                                                         240
                                                                         300
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
ggcactacca gcaacgtcag ggaagtgctc agccattgtg gtgtacacca aggcgaccac
                                                                         360
agcagetgen aceteageaa tgaagatgan gaggangatg aagaagaacg tenegaggge
                                                                         420
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna
                                                                         480
cnccggctgc gatgaagaaa tnaccccncg ttgacaaact tgcatggcac tggganccac
                                                                         540
agtggcccna aaaatcttca aaaaggatgc cccatcnatt gaccccccaa atgcccactg
                                                                         600
                                                                         660
ccaacagggg ctgcccacn cncnnaacga tganccnatt gnacaagatc tncntggtct
tnatnaacht gaaccetgen tngtggetee tgtteaggne ennggeetga ettetnaann
                                                                         720
aangaacten gaagneecca enggananne g
                                                                         751
      <210> 13
      <211> 729
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(729)
      <223> n = A, T, C or G
      <400> 13
gagecaggeg teectetgee tgeecactea gtggcaacac cegggagetg ttttgteett
                                                                          60
tgtggancet cagcagtnee etettteaga acteantgce aaganeeetg aacaggagee
                                                                         120
                                                                         180
accatgcagt getteagett cattaagace atgatgatee tetteaattt geteatettt
ctgtgtggtg cagccctgtt ggcagtgggc atctgggtgt caatcgatgg ggcatccttt
                                                                         240
ctgaagatct tcgggccact gtcgtccagt gccatgcagt ttgtcaacgt gggctacttc ctcatcgcag ccggcgttgt ggtcttagct ctaggtttcc tgggctgcta tggtgctaag
                                                                         300
                                                                         360
actgagagea agtgtgcct cgtgacgttc ttcttcatcc tcctcctcat cttcattgct
                                                                         420
gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt
                                                                         480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt
                                                                         540
gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacggatttt
                                                                         600
                                                                         660
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa
                                                                         720
                                                                         729
attnaaggg
      <210> 14
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (816)
      <223> n = A, T, C or G
      <400> 14
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcgcag
                                                                          60
tgttcgctga aggggttgta gtaccagcgc gggatgctct ccttgcagag tcctgtgtct
                                                                         120
ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcgtcaaag
                                                                         180
ccactegtgt attitteaca ggcageeteg tecgaegegt eggggeagtt gggggtgtet
                                                                         240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga
                                                                         300
                                                                         360
cangigecag ageacacigg atggegeett tecatgnnan gggeeetgng ggaaagteee
tganccccan anctgcctct caaangcccc accttgcaca ccccgacagg ctagaatgga
                                                                         420
atottottoo ogaaaggtag tintiottgt tgoocaanoo ancocontaa acaaactott
                                                                         480
                                                                         540
gcanatctgc tccgnggggg tcntantacc ancgtgggaa aagaacccca ggcngcgaac
                                                                         600
caancttgtt tggatncgaa gcnataatct nctnttctgc ttggtggaca gcaccantna
```

```
660
ctgtnnanct ttagncentg gteetentgg gttgnnettg aacetaaten cennteaact
gggacaaggt aantngcent cetttnaatt ceenanentn ceeeetggtt tggggttttn
                                                                             720
                                                                             780
chenetecta ceccagaaan necqtqttee cecccaacta qqqqeenaaa cennttntte
                                                                             816
cacaaccctn ccccacccac gggttcngnt ggttng
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(783)
      <223> n = A,T,C or G
      <400> 15
                                                                              60
ccaaggeetg ggcaggeata nacttgaagg tacaacccca ggaacccctg gtgetgaagg
                                                                             120
atqtqqaaaa cacaqattqq cqcctactqc qqqqtqacac qqatqtcaqq gtagaqaqga
aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga
                                                                              180
cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca
                                                                             240
ccaaqcaqac agaaqactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                             300
teccaegetg gtactatgae eccaeggage agatetgeaa gagtttegtt tatggagget
                                                                              360°
gettgggcaa caagaacaac tacetteggg aagaagagtg cattetance tgtengggtg
                                                                              420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct
                                                                              480
ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                              540
ncaatqqctq ctqcatcnac antttcctng aattgtgaca acacccccca ntgcccccaa
                                                                              600
ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacncccgg
                                                                              660
cncctccntt ttccccnntn aacaaagggc nctngcnttt gaactgcccn aacccnggaa
                                                                             720
                                                                             780
tetneening aaaaantice eccetqqtt cetniaance ecteenenaa anetneecee
                                                                             783
CCC
      <210> 16
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (801)
      <223> n = A, T, C or G
      <400> 16
                                                                               60
qccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
agetgattga ageaaceete taetttttgg tegtgageet tttgettggt geaggtttea
                                                                              120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                              180
                                                                              240
auqtaqqqtq aqtcctcaaa atccqtataq ttgqtqaaqc cacaqcactt gagccctttc
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
                                                                              300
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
                                                                              360
                                                                              420
cacttgctct ccgtcttagc accatagcag cccangaaac caagagcaaa gaccacaacg
                                                                              480
                                                                              540
conquique atquaaqaaa ntacccacgt tgacaaactg catggccact ggacgacagt
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
                                                                              600
cnacaggget geneenenen gaaagaatga gecattgaag aaggatente ntggtettaa tgaaetgaaa centgeatgg tggeeeetgt teagggetet tggeagtgaa ttetganaaa aaggaaenge ntnageeeee ceaaangana aaacaeeeee gggtgttgee etgaattgge
                                                                              660
                                                                              720
                                                                              780
                                                                              801
ggccaaggan ccctgccccn g
      <210> 17
      <211> 740
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc_feature
      \langle 222 \rangle (1) ... (740)
      <223> n = A, T, C or G
      <400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccggga gctgttttgt
                                                                             60
cctttgtgga gcctcagcag ttccctcttt cagaactcac tgccaagagc cctgaacagg
                                                                           120
agecaccatg cagtgettea getteattaa gaccatgatg atcetettea atttgeteat
                                                                           180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                           240
ctttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta
                                                                           300
cttcctcatc gcagccggcg ttgtggtctt tgctcttggt ttcctgggct gctatggtgc
                                                                           360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat
                                                                           420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc
                                                                           480
                                                                           540
aantntggaa caccnccatg aaaagggete caatttetgn tggetteece aactataceg
                                                                           600
gaatttigaa aganteneee taetteeaaa aaaaaanant tgeetttnee eeenttetgi
                                                                           660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                           720
caaaaaaant nnaagggttn
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(802)
      <223> n = A, T, C or G
      <400> 18
ccgctggttg cgctggtcca gngnagccac gaagcacgtc agcatacaca gcctcaatca
                                                                             60
caaggtette cagetgeege acattaegea gggcaagage etecageaac actgeatatg
                                                                           120
ggatacactt tactttaqca gccagggtga caactgagag gtgtcgaagc ttattcttct
                                                                           180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat
                                                                           240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                           300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                           360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                           420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                           480
gctcaggatg tccagagacg tggttccgcc ccctcnctta atgacaccgn ccanncaacc
                                                                           540
gteggetece geegantgng ttegtegtne etgggteagg gtetgetgge enetaettge
                                                                           600
aancttegte nggeeeatgg aatteacene aceggaactn gtangateea etnnttetat aaceggnege cacegennnt ggaacteeae tettnttnee tttaettgag ggttaaggte
                                                                           660
                                                                           720
accettnncg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                           780
tnccancene atangaagee ng
                                                                           802
      <210> 19
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (731)
      <223> n = A, T, C or G
      <400> 19
cnaagettee aggtnaeggg cegenaance tgaceenagg tancanaang cagnengegg
                                                                            60
gageceaceg teacgnggng gngtetttat nggaggggge ggagecacat enetggaent
                                                                           120
entgacecca acteceence neneantgea gtgatgagtg cagaactgaa ggtnacgtgg
                                                                           180
                                                                           240
caggaaccaa gancaaanne tgeteennte caagteggen nagggggegg ggetggecae
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                           300
```

```
360
catgcccagn gttanataac nggcngagag tnantttgcc tctcccttcc ggctgcgcan
                                                                        420
cgnqtntqct tagnqgacat aacctgacta cttaactgaa cccnngaatc tnccncccct
ccactaaget cagaacaaaa aacttegaca ccactcantt gtcacetgnc tgctcaagta
                                                                        480
aagtgtaccc catneccaat gtntgctnga ngctctgncc tgcnttangt tcggtcctgg
                                                                        540
gaagacetat caattnaage tatgittetg actgeetett geteeetgna acaanenace
                                                                        600
cnncnntcca aggggggnc ggccccaat cccccaacc ntnaattnan tttancccn
                                                                        660
                                                                        720
cccccnggcc cggcctttta cnancntcnn nnacngggna aaaccnnngc tttncccaac
nnaatccncc t
                                                                        731
      <210> 20
      <211> 754
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (754)
      <223> n = A, T, C or G
      <400> 20
ttttttttt tttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc
                                                                         60
                                                                        120
caacccctc ntccaaatnn contttccgg gngggggttc caaacccaan ttanntttgg
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                        180
                                                                        240
tnancttnaa tncctggaaa congtngntt ccaaaaatnt ttaaccetta anteceteeg
                                                                        300
aaatngttna nggaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa ggnnancccc ggttantnaa tccccccnnc cccaattata ccgantttt ttngaattgg
                                                                        360
                                                                        420
ganceenegg gaattaaegg ggnnnnteee tnttgggggg enggnneece eccenteggg
                                                                        480
ggttngggnc aggncnnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc
                                                                        540
                                                                        600
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
ggggcctggg atttinttc ccctnttncc tccccccc ccnggganag aggtingngt
                                                                        660
tttgntenne ggeceeneen aaganetttn eeganttnan ttaaateent geetnggega
                                                                        720
agtccnttgn agggntaaan ggccccctnn cggg
                                                                        754
      <210> 21
      <211> 755
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(755)
      <223> n = A, T, C or G
                                                                         60
atcancecat gacceenaac nngggacene teanceggne nnnenacene eggeenatea
nngtnagnnc actnonnttn natcacnocc encenactae gecenenane enacgeneta
                                                                        120
nncanatnce actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn
                                                                        180
                                                                        240
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattn
                                                                        300
nnenneanat gatttteetn anecgattae centneecee taneceetee eececaaena
cgaaggenet ggneenaagg nngegnenee eegetagnte eeenneaagt eneneneeta
                                                                        360
aacteancen nattacnege ttentgagta teacteeceg aateteacee tacteaacte
                                                                        420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt
                                                                        480
ttagnggtcc ntnaanchtc ctaatacttc cagtctncct tcnccaattt ccnaanggct
                                                                        540
ctttengaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttentngaac
                                                                        600
gggctentet ttteettegg ttancetggn ttenneegge eagttattat tteeentttt
                                                                        660
                                                                        720
aaattentne entttanttt tggenttena aacceegge ettgaaaaeg geeceetggt
                                                                        755
aaaaggttgt tttganaaaa tttttgtttt gttcc
      <210> 22
      <211> 849
      <212> DNA
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
       <222> (1) ... (849)
      <223> n = A, T, C or G
                                                                               60
ttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt
acgctnggan taangcgacc cganttctag gannencect aaaatcanac tgtgaagatn atectgnnna cggaanggte accggnngat nntgetaggg tgncenetee cannnenttn
                                                                              120
                                                                              180
cataacteng nggccetgcc caccacette ggcggcceng ngnccgggcc cgggtcattn
                                                                              240
gnnttaaccn cactnigena neggttteen neecenneng accenggega teeggggtne
                                                                              300
tetgtettee cetgnagnen anaaantggg ceneggneee etttacecet nnacaageea
                                                                              360
engeenteta neenengeee eeceteeant nngggggaet geenannget eegttnetng
                                                                              420
nnaccconnn gggtncctcg gttgtcgant cnaccgnang ccanggattc cnaaggaagg tgcgttnttg gcccctaccc ttcgctncgg nncacccttc ccgacnanga nccgctcccg
                                                                              480
                                                                              540
enennegning cetenceteg caacaceege netentengt neggninece ecceaeeege
                                                                              600
necetenene ngnegnanen eteeneenee gteteannea ecaeceegee eegeeaggee
                                                                              660
ntcanccacn ggnngacnng nagenennte geneegegen gegneneeet egeenengaa
                                                                              720
ctncntcngg ccantnncgc tcaanconna cnaaacgccg ctgcgcggcc cgnagcgncc
                                                                              780
necteenega gteeteeeqn etteenacee angnntteen egaggaeaen nnaceeegee
                                                                              840
nncangcgg
                                                                              849
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (872)
      <223> n = A, T, C or G
      <400> 23
gegeaaacta tacttegete gnactegtge geetegetne tetttteete egeaaceatg
                                                                               60
                                                                              120
tetgacnane eegattngge ngatatenan aagntegane agteeaaaet gantaacaca
cacacnenan aganaaatee netgeettee anagtanaen attgaaenng agaaceange
                                                                              180
                                                                              240
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccagcntcnc
ctncenacce tacntetten nagetgtenn acceetngtn egnaceeece naggteggga
                                                                              300
tegggtttnn nntgacegng enneceetee eccenteeat nacganeene eegeaceaee
                                                                              360
                                                                              420
nanngcnege neceegnnet ettegeence etgteetntn cecetgtnge etggenengn
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                              480
tgggnnngeg tetgeneege gtteetteen nennetteea eeatettent taengggtet
                                                                              540
congeente tennneache cetgggaege thteethtge ecceetthae tecceeett
                                                                              600
cqncqtqncc cqncccacc ntcatttnca nacqntcttc acaannncct qqntnnctcc
                                                                              660
chanchgnen gteanechag ggaagggngg ggnneenntg nttgaegttg nggngangte egaanantee teneentean enetaceet egggegnnet etengttnee aaettaneaa
                                                                              720
                                                                              780
ntetececeg agagemente teageetene ceneceenet etetgeantg thetetgete
                                                                              840
tnaccnntac gantnttcgn cnccctcttt cc
                                                                              872
      <210> 24
      <211> 815
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (815)
      <223> n = A, T, C or G
      <400> 24
```

PCT/US00/27464

660

```
qcatqcaaqc ttqaqtattc tataqnqtca cctaaatanc ttqqcntaat catqqtcnta
                                                                         .60
nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta
                                                                         120
                                                                         180
tentneatta gtaacaantg tnntgteeat cetgtengan canatteeca tnnattnegn
cgcattcncn gcncantatn taatngggaa ntcnnntnnn ncaccnncat ctatcntncc
                                                                         240
geneeetgae tggnagagat ggatnantte tnntntgace nacatgttea tettggattn
                                                                         300
aanancecee egengneeae eggttngnng enageennte eeaagacete etgtggaggt
                                                                         360
aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaagt ngnnncanan
                                                                         420
gatecegtee aggnttnace atceettene agegeeect tingtgeett anagngnage
                                                                         480
                                                                         540
gtgtccnanc cnctcaacat ganacgcgcc agnccanccg caattnggca caatgtcgnc
gaacccccta gggggantna thcaaanccc caggattgtc chencangaa atccchcanc
                                                                         600
cccnccctac ccnnctttgg gacngtgacc aantcccgga gtnccagtcc ggccngnctc
                                                                         660
ccccaccggt nnccntgggg gggtgaanct cngnntcanc cngncgaggn ntcgnaagga
                                                                         720
accggneetn ggnegaanng anenntenga agngeenent egtataacce ecceteneea
                                                                         780
nccnacngnt agntcccccc engggtnegg aangg
                                                                         815
      <210> 25
      <211> 775
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (775)
      <223> n = A, T, C or G
      <400> 25
ccgagatgtc tcgctccgtg gccttagctg tgctcgcgct actctcttt tctggcctgg
                                                                          60
aggetateca gegtaeteca aagatteagg tttaeteacg teatecagea gagaatggaa
                                                                         120
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgact
                                                                         180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                         240
                                                                         300
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                         360
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt
                                                                         420
ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat gnccccaaat
                                                                         480
tgtaggggtt acatnantgt tenentngga catgatette etttataant cencentteg
                                                                         540
aattgcccgt cncccngttn ngaatgtttc cnnaaccacg gttggctccc ccaggtcncc
                                                                         600
tettaeggaa gggeetggge enetttneaa ggttggggga accnaaaatt tenettntge eeneceneea enntettgng nneneanttt ggaaceette enatteeeet tggeetenna
                                                                         660
                                                                         720
nccttnncta anaaaacttn aaancgtngc naaanntttn acttcccccc ttacc
                                                                         775
      <210> 26
      <211> 820
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (820)
      <223> n = A, T, C \text{ or } G
      <400> 26
anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
                                                                         60
cccanagata ncttatanca acagtgcttt gaccaagagc tgctgggcac atttcctgca
                                                                        120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                         180
ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca
                                                                        240
ntgatgacca tgggcgggag cgagcctctt ccctgnaccg gggtggcana nganagccta
                                                                         300
nctgagggt cacactataa acgttaacga ccnagatnan cacctgcttc aagtgcaccc
                                                                        360
ttcctacctg acnaccagng accnnnaact gengeetggg gacagenetg ggancageta
                                                                        420
acnnageact cacetgeece eccatggeeg inegenteec iggicetgne aagggaaget
                                                                        480
ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                        540
gatggaattt thecetteeg geennteece tetteettta caegeeecet nntactente
                                                                        600
tecetetntt nteetgnene actitinace commattic ectinatiga teggannetn
```

```
720
 ganattecae threegethe entenating naanachaaa nacthtetha ceenggggat
 gggnnected ntcatectet etttttenet aceneenntt etttgeetet cettngatea
780tccaacente gntggeentn ecceceennn teetttneee
820
             <210> 27
             <211> 818
             <212> DNA
             <213> Homo sapien
             <220>
        <221> misc_feature
             <222> (1)...(818)
             <223> n = A, T, C or G
             <400> 27
 totgggtgat ggcctcttcc tcctcaggga cctctgactg ctctgggcca aagaatctct
                                                                                                                                            60
 tgtttcttct ccgagcccca ggcagcggtg attcagccct gcccaacctg attctgatga
                                                                                                                                          120
 ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                                                                                          180
 ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct gggctgggtc
                                                                                                                                          240
 tecgeeteea qggttetget ettecangea ngecancaag tggegetggg ceacactgge
                                                                                                                                          300
 ttetteetge ecentecetg getetgante tetgtettee tgteetgige angeneettg
                                                                                                                                          360
 gateteagtt teeetenete anngaactet gtttetgann tetteantta actntgantt
                                                                                                                                          420
 tatnacenan tggnetgtne tgtennactt taatgggeen gaeeggetaa teeeteeete
                                                                                                                                          480
 netecettee anttennna accegettee ententetee centaneceg eengggaane
                                                                                                                                          540
 cteetttgee etnaceangg geennnaceg ecentnnetn ggggggenng gtnnetnene etgntnnece enetenennt tneetegtee ennennegen nngeanntte nengteeenn
                                                                                                                                          600
                                                                                                                                          660
 tnnctctten ngtntegnaa ngntenentn tnnnnngnen ngntnntnen teeetetene
                                                                                                                                          720
 connitging that the new control of the control of t
                                                                                                                                          780
 cccnnccccc ngnattaagg cctccnntct ccggccnc
                                                                                                                                          818
             <210> 28
             <211> 731
             <212> DNA
             <213> Homo sapien
             <220>
             <221> misc_feature
             <222> (1) ... (731)
             <223> n = A, T, C or G
             <400> 28
 aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg
                                                                                                                                            60
 toccaacatg anggtgnngt totottttga angagggttg ngtttttann conggtgggt
                                                                                                                                          120
 gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcagtat
                                                                                                                                          180
                                                                                                                                          240
 ntanatteet ginaategga aaatnainti tennenggaa aaintigete eeateegnaa
 attnetcccg ggtagtgcat nttngggggn cngccangtt tcccaggctg ctanaatcgt
                                                                                                                                          300
 actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatccn tacccgactg
                                                                                                                                          360
 tnnnttnect tegecetntg actetgenng ageceaatae cenngngnat gtenecengn
                                                                                                                                          420
 nnngcgncnc tgaaannnnc tcgnggctnn gancatcang gggtttcgca tcaaaagcnn
                                                                                                                                          480
 egttteneat naaggeactt tngeeteate caacenetng eeetenneea tttngeegte
                                                                                                                                          540
                                                                                                                                          600
 nggtteneet aegetnntng encetnnntn ganattttne eegeetnggg naanceteet
 gnaatgggta gggncttntc ttttnaccnn gnggtntact aatennetne acgentnett
                                                                                                                                          660
 tetenacee eccetttt caateecane ggenaatggg gteteecenn egangggggg
                                                                                                                                          720
 nnncccannc c
                                                                                                                                          731
             <210> 29
             <211> 822
             <212> DNA
             <213> Homo sapien
             <220>
```

```
<221> misc feature
      <222> (1) ... (822)
      <223> n = A, T, C or G
      <400> 29
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat
                                                                            60
cgctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncnnt
                                                                           120
aththtache teatanneet ennnaceeae teeetettaa eeentaetgt geetatngen
                                                                           180
                                                                           240
tnnctantct ntgccgcctn cnanceaccn gtgggccnac cncnngnatt ctcnatctcc
tenecatntn geetananta ngtneatace etatacetae necaatgeta nnnetaanen
                                                                            300
tccatnantt annntaacta ccactgacnt ngactttene atnanctect aatttgaate
                                                                           360
tactctgact cccacngcct annuattagc anentocccc nacnatntct caaccaaatc
                                                                            420
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aaccccctc
                                                                            480
ccaaataccc nccacctgac ncctaacccn caccatcccg gcaagccnan ggncatttan
                                                                            540
                                                                            600
ccactggaat cacnatngga naaaaaaac cenaactete tanenennat etecetaana
                                                                            660
aatnotootn naatttactn noantnooat caanoocacn tgaaacnnaa cocctgtttt
tanatecett etttegaaaa eenaceettt annneecaae etttngggee eeceenetne
                                                                           720
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
                                                                           780
canatectat cecttanttn ggggneeett neeengggee ee
                                                                           822
      <210> 30
<211> 787
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (787)
      <223> n = A, T, C \text{ or } G
      <400> 30
cggccgcctg ctctggcaca tgcctcctga atggcatcaa aagtgatgga ctgcccattg
                                                                            60
ctagagaaga cettetete tactgteatt atggageeet geagactgag ggeteeeett gtetgeagga tttgatgtet gaagtegtgg agtgtggett ggageteete atetacatna
                                                                            120
                                                                           180
gctggaagcc ctggaggcc tctctcgcca gcctcccct tctctccacg ctctccangg
                                                                            240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
                                                                            300
cccatggggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctggca
                                                                            360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagete cagetttgt tcccnttaat gaaggttaat tgcncgcttg gcgtaatcat nggtcanaac tntttcctgt
                                                                            420
                                                                            480
gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt
                                                                            540
taaaqcctqq qqqtnqcctn nnqaatnaac tnaactcaat taattqcqtt qqctcatqqc
                                                                            600
                                                                            660
ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca cccccnggg
aaaageggtt tgenttttng ggggnteett cenetteece eetenetaan eeetnegeet
                                                                            720
eggtegttne nggtngeggg gaangggnat nnnetecene naagggggng agnnngntat
                                                                            780
                                                                            787
ccccaaa
      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(799)
      <223> n = A, T, C or G
      <400> 31
                                                                            60
tttttttttt tttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac
                                                                           120
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc
aacaaaggac tcctgcagcc ttctctgtct gtctcttggc gcaggcacat ggggaggcct
                                                                           180
                                                                           240
cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                           300
```

```
360
qqqqaccttc tqttctccca nqqnaacttc ntnnatctcn aaagaacaca actgtttctt
cngcanttct ggctgttcat ggaaagcaca ggtgtccnat ttnggctggg acttggtaca
                                                                         420
tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctnttg
                                                                         480
cctqqqcct taantacca caccqqaact canttantta ttcatcting gntgggcttg
                                                                         540
ntnateneen eetgaangeg eeaagttgaa aggeeaegee gtneeenete eecatagnan
                                                                         600
nttttnnent canctaatge ceeceengge aacnatecaa teeceeceen tgggggeece
                                                                         660
                                                                         720
ageceangge eccequateg ggnnneengn enegnantee ecaggntete ecantengne
connigence ecceptace gaacanaage ntngageene egeannninn negtinienae
                                                                         780
                                                                         799
ctcgccccc ccnncgnng
      <210> 32
      <211> 789
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (789)
      <223> n = A, T, C or G
tttttttt tttttttt
                                                                          60
ttttnccnaq qqcaqqttta ttqacaacct cncqqqacac aancaqqctq qqqacaqqac
                                                                         120
                                                                         180
ggcaacaggc tccggcggcg gcggcggcgg ccctacctgc ggtaccaaat ntgcagcctc
                                                                         240
cgctcccgct tgatnttcct ctgcagctgc aggatgccnt aaaacagggc ctcggccntn
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc nattaggaat agtggtntta cccnccnccg ttggcncact ccccntggaa accacttntc
                                                                         300
                                                                         360
geggeteegg catetggtet taaacettge aaacnetggg geeetetttt tggttantnt
                                                                         420
ncengecaca atcatnacte agactggene gggetggece caaaaaanen eeccaaaace
                                                                         480
                                                                         540
ggnccatgte ttnneggggt tgctgcnatn tncatcacct cccgggcnca ncaggncaac
                                                                         600
ccaaaagttc ttgnggcccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
ccccttggcc cccaaatcct cccccgntt nctgggtttg ggaacccacg cctctnnctt tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
                                                                         660
                                                                         720
ntectnnnca ceatecece nngnnaegne tancaangna teeettttt tanaaaeggg
                                                                         780
cccccncg
                                                                         789
      <210> 33
      <211> 793
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(793)
      <223> n = A.T.C or G
      <400> 33
qacagaacat gttggatggt ggagcacctt tctatacgac ttacaggaca gcagatgggg
                                                                          60
                                                                         120
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg
                                                                         180
gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana
                                                                         240
aqaaqtttqc agatqtattt qcaaaqaaga cgaagqcaga gtggtqtcaa atctttgacg
                                                                         300
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac
                                                                         360
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
                                                                         420
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct
                                                                         480
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac
                                                                         540
                                                                         600
acaacatacq anccqqaaqc atnaaatttt aaaqcctgqn ggtngcctaa tgantgaact
nactcacatt aattggcttt gegeteactg eccgetttee agteeggaaa acctgteett
                                                                         660
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttgggg
                                                                         720
egenettece getttetege tteetgaant cetteecece ggtetttegg ettgeggena
                                                                         780
                                                                         793
acggtatcna cct
```

PCT/US00/27464 WO 01/25272

15

```
<210> 34
       <211> 756
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(756)
       <223> n = A, T, C or G
       <400> 34
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt
                                                                                  60
ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg
                                                                                 120
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag
                                                                                 180
atoggggcc aatggagcat cctacgcaan gacatccct ccttcgagcg ctacatggcc
                                                                                 240
cageteaaat getaetaett tgattacaan gageagetee eegagteage etatatgeae eagetettgg geeteaaeet eetetteetg etgteeeaga aeegggtgge tgantneeae
                                                                                 300
                                                                                 360
acgganttgg ancggetgee tgeecaanga catacanace aatgtetaca tenaceacea
                                                                                 420
gtqtcctqqa qcaatactqa tqqanqqcaq ctaccncaaa qtnttcctqq ccnaqqqtaa
                                                                                 480
catecoccgc egagagetac acettettea ttgacatect getegacact atcagggatg
                                                                                 540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggccccgg
                                                                                 600
athenetagt netagaateg geoegecate geggtggane etceaacett tegttheect ttactgaggg ttnattgeeg eeettggegt tateatggte acheengtth eetgtttga
                                                                                 660
                                                                                 720
aattnttaac ccccacaat tccacgccna cattng
                                                                                 756
       <210> 35
       <211> 834
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(834)
       <223> n = A, T, C or G
       <400> 35
ggggatetet anatenacet gnatgeatgg ttgteggtgt ggtegetgte gatgaanatg
                                                                                  60
aacaggatet tgecettgaa getetegget getgtnttta agttgeteag tetgeegtea
                                                                                 120
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat
                                                                                 180
aatettengg getgtetget eggtgaacte gatgaenang ggeagetggt tgtgtntgat
                                                                                 240
agantecane angitetect tggtgacete ecetteaaag ttgtteegge etteateaaa
                                                                                 300
cttctnnaan angannance canctttgte gagetggnat ttgganaaca cqtcactgtt
                                                                                 360
                                                                                 420
ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt
ggencaaate egacteeen teettgaaag aageenatea caceeeete eetggaetee nncaangaet etneegetne eeenteenng eagggttggt ggeanneegg geeentgege teetteagee agtteaenat ntteateage eeetetgeea getgttntat teettggggg
                                                                                 480
                                                                                 540
                                                                                 600
ggaanccgtc tctcccttcc tgaannaact ttgaccgtng gaatagccgc gcntcnccnt
                                                                                 660
acninctggg ccgggttcaa anteceteen tignennien ectcgggeca tietggatti
                                                                                 720
nccnaacttt ttccttcccc cnccccncgg ngtttggntt tttcatnggg ccccaactct
                                                                                 780
getnttggcc anteceetgg gggentntan enceceetnt ggtecentng ggce
                                                                                 834
       <210> 36
       <211> 814
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(814)
       <223> n = A, T, C \text{ or } G
```

<400> 36

```
60
cggncgcttt ccngccgcgc cccgtttcca tgacnaaggc tcccttcang ttaaatacnn
                                                                        120
cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgccca
naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc acccctgta
                                                                       180
ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaagtctt gtgttttact
                                                                       240
                                                                        300
aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg cagcctggca
ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca
                                                                        360
ggcttgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttgtc
                                                                        420
antganctqq aaggeetqaa nettagtete caaaagtete ngeecacaag aceggeeace
                                                                        480
aggggangte ntttncagtg gatetgccaa anantaccen tateatennt gaataaaaag
                                                                       540
qcccctqaac qanatqcttc cancancctt taaqacccat aatcctngaa ccatggtgcc
                                                                        600
cttccggtct gatccnaaag gaatgttcct gggtcccant ccctcctttg ttncttacgt
                                                                        660
                                                                        720
tgtnttqqac ccntqctnqn atnacccaan tganatcccc ngaagcaccc tncccctggc
                                                                       780
atttganttt cntaaattet etgeeetaen netgaaagea enatteeetn ggeneenaan
ggngaactca agaaggtctn ngaaaaacca cncn
                                                                       814
      <210> 37
      <211> 760
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (760)
      <223> n = A, T, C or G
gcatgctgct cttcctcaaa gttgttcttg ttgccataac aaccaccata ggtaaagcgg
                                                                        60
                                                                       120
qcqcaqtqtt cqctqaaqqq qttqtaqtac cagcqcggga tqctctcctt gcaqaqtcct
gtgtctggca ggtccacgca atgccctttg tcactgggga aatggatgcg ctggagctcg
                                                                       180
                                                                        240
tenaanceae tegtgtattt tteacangea geeteeteeg aagenteegg geagttgggg
gtgtcgtcac actccactaa actgtcgatn cancagccca ttgctgcagc ggaactgggt
                                                                       300
gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat
                                                                        360
cnectnance caaactgeet etcaaaggee acettgeaca ceeegacagg etagaaatge
                                                                        420
actettette ecaaaggtag ttgttettgt tgeecaagea neetecanea aaccaaaane
                                                                        480
ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn
                                                                        540
gancenectt gtttgaatge naaggnaata atceteetgt ettgettggg tggaanagea
                                                                       600
caattgaact gttaachttg ggccgngtte enetngggtg gtetgaaact aatcacegte
                                                                       660
actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctngntt tgggtnnttt
                                                                       720
ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg
                                                                       760
      <210> 38 <211> 724
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (724)
      \langle 223 \rangle n = A, T, C or G
      <400> 38
ttttttttt tttttttt tttttttt tttttaaaaa ccccctccat tgaatgaaaa
                                                                        60
                                                                       120
cttccnaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc
caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa
                                                                       180
aatttaaccc attatnaact taaatnoctn gaaacccntg gnttccaaaa atttttaacc
                                                                       240
                                                                       300
cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt
                                                                       360
ngatttaaac ccccttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt
tcctnttaan cntnggtaac tcccgntaat gaannnccct aanccaatta aaccgaattt
                                                                       420
tttttgaatt ggaaattccn ngggaattna ccggggtttt tcccntttgg gggccatncc
                                                                       480
                                                                       540
cccnctttcg gggtttgggn ntaggttgaa ttittnnang ncccaaaaaa ncccccaana
                                                                       600
aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg
                                                                       660
tttntggggg congggantt onttoccoon ttnconcooc coccoonggt aaanggttat
```

```
720
ngnntttggt ttttqggccc cttnanggac cttccggatn gaaattaaat ccccgggncg
                                                                              724
gccg
      <210> 39
      <211> 751
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (751)
      <223> n = A, T, C or G
      <400> 39
tttttttttt tttttctttg ctcacattta atttttattt tgatttttt taatgctgca
                                                                               60
caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctgctgt
                                                                              120
tttatttatt tttactgaaa gtgagaggga acttttgtgg ccttttttcc tttttctgta
                                                                              180
                                                                              240
ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt.
                                                                              300
cgcaaaatca ctcgggggaa nggaaaggtt gctttgttaa tcatgcccta tggtgggtga
ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana
                                                                              360
cttqqqqqtt ccctcccan accaacccn ctqacaaaaa qtqccnqccc tcaaatnatg
                                                                              420
tcccggcnnt cnttgaaaca cacngcngaa ngttctcatt ntccccncnc caggtnaaaa
                                                                              480
tgaaqqqtta ccatntttaa cnccacctcc acntgqcnnn gcctgaatcc tcnaaaancn
                                                                              540
cecteaanen aattnetnng ecceggtene gentnngtee eneeeggget eegggaantn caceceenga annenntnne naacnaaatt eegaaaatat teeenntene teaatteeee
                                                                              600
                                                                              660
cnnagactnt cctcnncnan cncaattttc ttttnntcac gaacnegnnc cnnaaaatgn
                                                                              720
                                                                              751
nnnncncctc cnctngtccn naatcnccan c
      <210> 40
      <211> 753
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (753)
      <223> n = A, T, C or G
                                                                               60
gtggtatttt ctgtaagatc aggtgttcct ccctcgtagg tttagaggaa acaccctcat
agatgaaaac ccccccgaga cagcagcact gcaactgcca agcagccggg gtaggagggg
                                                                              120
cgccctatgc acagctgggc ccttgagaca gcagggcttc gatgtcaggc tcgatgtcaa tggtctggaa gcggcggctg tacctgcgta ggggcacacc gtcagggccc accaggaact
                                                                              180
                                                                              240
totcaaagtt ccaggcaach togttgcgac acaccggaga ccaggtgath agottggggt
                                                                              300
                                                                              360
cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctcccgc aggaaggcna
ataaaaggtg cgccccgca ccgttcanct cgcacttctc naanaccatg angttgggct
                                                                              420
cnaacccacc accanneegg actteettga nggaatteec aaatetette gntettggge
                                                                              480
ttctnctgat gccctanctg gttgcccngn atgccaanca nccccaance ccggggtcct aaancacccn cctcctcntt tcatctgggt tnttntcccc ggaccntggt tcctctcaag
                                                                             540
                                                                              600
qqancccata tetenaecan tacteaecnt neceeecent gnnaeceane ettetanngn
                                                                              660
                                                                             720
ttcccncccg ncctctggcc cntcaaanan gcttncacna cctgggtctg ccttccccc
                                                                              753
tnccctatct gnacccenen tttgtctcan tnt
      <210> 41
      <211> 341
      <212> DNA
      <213> Homo sapien
actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaatg
                                                                              60
agtgaaccca toottgattt atatacatat atgttotcag tattttggga gootttocac
                                                                             120
                                                                             180
ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt
```

tatagcttgt ttacgtagta agtttttgaa tgttaaactg tgatttttaa aaaatatcat ttttactttt tgattaattg tgttttatat	ttgagaatat	tctttcagag	cttagttgag gtattttcat	240 300 341
<210> 42 <211> 101 <212> DNA <213> Homo sapien				
<400> 42 acttactgaa tttagttctg tgctcttcct gtttcaaaca ttctaaataa ataattttca			atactttgat	60 101
<210> 43 <211> 305 <212> DNA <213> Homo sapien				
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<210> 44 <211> 852 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(852) <223> n = A,T,C or G				
<pre>&lt;400&gt; 44 acataaatat cagagaaaag tagtcttga gattattgg tgtgtgttt ggtttgtgtc ctctccatcc tcgggcattc ttcccaaatt ccagaattc tcttttgtag taatactca tgctgttgtt cttctttta ccccatagct agacgccctc agatcggtct tcccattta ggatgtcgcg gatgaattcc cataagtgag acttggcagg ggggtcttgc tccttttca tggtggttgt catggagatc tgagcccggc tgctaccata gttggtgtca tataaatagt gctcagtttg ttcagtcttg acaatgacat actggccgt ccacttcaga tgctgcaagt ccgcccgggt gaactcctgc aaactcatgc cntggaaagg gatacaattg gcatccagct cccacacctg gt</pre>	caaagtattg tatataccag tagctcggct gagccactgc ttaatcctgg tccctctcgg tatcaggtga agaaagtttt tctngtcttt tgtgtgtgga tgctgtagag tgcaaaggtg	gcagcttcag tcttcgtcca gagcttttca ctctgattc gttcttgtct gttgtgcttt ctctgcaaca gctgtccaac ccaggtgttc ctggaacagg gagntgccc ctcgccgttg	ttttcatttt tccacacgct taggtcatgc aagaacctga gggttcaaga ttggtgtggc ggaaggtgac aaatctactg atgatggaag tcactactgc gccgtccctg atgtcgaact	60 120 180 240 300 360 420 480 540 660 720 780 840 852
<210> 45 <211> 234 <212> DNA <213> Homo sapien				
<pre>&lt;400&gt; 45 acaacagacc cttgctcgct aacgacctca agtctgacac catccggagc atcagcattg gcctcgtttc tggctgggt ctgctggcga</pre>	cttcgcagtg	ccctaccgcg	gggaactctt	60 120 180

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tgaacgtgtc ggtggtqtct gaggaggtct gcagtaagct ctatgacccg ctgt
                                                                           234
      <210> 46
      <211> 590
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (590)
      <223> n = A, T, C or G
      <400> 46
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                                                                             60
atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa
                                                                            120
aagaagataa tatattccaa gcanatacaa aatatctaat gaaagatcaa ggcaggaaaa
                                                                            180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                            240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat
                                                                            300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                            360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                            420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
                                                                            480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
                                                                            540
gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt
                                                                            590
      <210> 47
      <211> 774
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (774)
      <223> n = A, T, C or G
      <400> 47
acaagggggc ataatgaagg agtggggana gattttaaag aaggaaaaaa aacgaggccc
                                                                             60
tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                            120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                            180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
                                                                            240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                            300
cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg
                                                                            360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc ccacactcct tgaacacaca tccccaggtt atattcctgg acatggctga acctcctatt
                                                                            420
                                                                            480
cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctccaaacc
                                                                            540
acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccttga
                                                                            600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct
                                                                            660
                                                                            720
tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                            774
      <210> 48
      <211> 124
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(124)
      <223> n = A, T, C or G
      <400> 48
canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt
                                                                             60
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact
                                                                           120
```

<213> Homo sapien

```
tggt
                                                                        124
      <210> 49
      <211> 147
      <212> DNA
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      <220>
      <221> misc_feature
      <222> (1)...(147)
      \langle 223 \rangle n = A, T, C or G
      <400> 49
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt
                                                                         60
tgtggctaca ggtggtgtct gactgcatna aaaantfttt tacgggtgat tgcaaaaatt
                                                                        120
ttagggcacc catatcccaa gcantgt
                                                                        147
      <210> 50
      <211> 107
      <212> DNA
      <213> Homo sapien
      <400> 50
acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatattgc
                                                                         60
                                                                        107
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt
      <210> 51
      <211> 204
      <212> DNA
      <213> Homo sapien
      <400> 51
gtcctaqqaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg
                                                                         60
cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag
                                                                        120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca
                                                                        180
                                                                        204
cctccctttt gggaccagca atgt
      <210> 52
      <211> 491
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (491)
      <223> n = A, T, C or G
      <400> 52
acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaaggtta gtattgtgta
                                                                         60
qqqtattttc caaaaqacta aaqaqataac tcaqqtaaaa agttaqaaat gtataaaaca
                                                                        120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa
                                                                        180
aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt
                                                                        240
                                                                        300
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcagtccca
                                                                        360
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc
atgcaacagt gtctttctt tncttttct ttttttttt ttacaggcac agaaactcat
                                                                        420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat
                                                                        480
                                                                        491
atcactcttg t
      <210> 53
      <211> 484
      <212> DNA
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PCT/US00/27464 WO 01/25272

21

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<220>
      <221> misc_feature
      <222> (1) ... (484)
      <223> n = A, T, C or G
      <400> 53
                                                                        60
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gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac
                                                                       120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct
                                                                       180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct
                                                                       240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                       300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                       360
                                                                       420
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg
                                                                       480
tancttgant cigtgtattc caggancagg cggatggaat gggccagccc ncggatgttc
                                                                       484
      <210> 54
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 54
actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg
                                                                        60
                                                                       120
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag
tctatgtcct ctcaagtgcc tttttgtttg t
                                                                       151
      <210> 55
      <211> 91
      <212> DNA
      <213> Homo sapien
      <400> 55
                                                                        60
acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc
                                                                        91
gccctccagt ggatactcga gccaaagtgg t
      <210> 56
      <211> 133
      <212> DNA
      <213> Homo sapien
      <400> 56
qqcqqatqtq cqttqqttat atacaaatat qtcattttat qtaaqqqact tqaqtatact
                                                                        60
                                                                       120
tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc
                                                                       133
aagggacaac tgt
      <210> 57
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(147)
      <223> n = A, T, C or G
      <400> 57
                                                                        60
actotggaga acctgageeg etgeteegee tetgggatga ggtgatgean gengtggege
gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana
                                                                       120
tctcantggg ctggatncat gcagggt
                                                                       147
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<210> 58

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<211> 198
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(198)
       <223> n = A, T, C or G
       <400> 58
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc
                                                                         60
 tgattacata catttatect ttaaaaaaga tgtaaatett aatttttatg eeatetatta
                                                                         120
 atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt
                                                                         180
 ttgacttcta agtttggt
                                                                         198
       <210> 59
       <211> 330
       <212> DNA
       <213> Homo sapien
       <400> 59
 acaacaaatg ggttgtgagg aagtcttatc agcaaaactg gtgatggcta ctgaaaagat
                                                                         60
 ccattgaaaa ttatcattaa tgattttaaa tgacaagtta tcaaaaactc actcaatttt
                                                                         120
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa
                                                                         180
 tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagacccag
                                                                         240
 cagaaggaat ctattttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt
                                                                         300
. tttcgtcttt attggacttc tttgaagagt
                                                                         330
       <210> 60
       <211> 175
       <212> DNA
       <213> Homo sapien
       <400> 60
 acceptgggtg ccttctacat tcctgacggc tccttcacca acatctggtt ctacttcggc
                                                                         60
 gtegtggget cetteetett cateeteate cagetggtge tgeteatega etttgegeae
                                                                         120
 tectggaace ageggtgget gggcaaggee gaggagtgeg attecegtge etggt
                                                                         175
       <210> 61
       <211> 154
       <212> DNA
       <213> Homo sapien
       <400> 61
 accecacttt teeteetgtg ageagtetgg actteteact getacatgat gagggtgagt
                                                                         60
 ggttgttgct cttcaacagt atcctccct ttccggatct gctgagccgg acagcagtgc
                                                                        120
 tggactgcac agccccgggg ctccacattg ctgt
                                                                        154
       <210> 62
       <211> 30
       <212> DNA
       <213> Homo sapien
       <400> 62
                                                                         30
 cgctcgagcc ctatagtgag tcgtattaga
       <210> 63
       <211> 89
       <212> DNA
       <213> Homo sapien
       <400> 63
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acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc ctgtatgaat aaaaatggtt atgtcaagt	60 89
<210> 64 <211> 97 <212> DNA <213> Homo sapien	
<400> 64 accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag aatcagtgca tccaggattg gtccttggat ctggggt	60 97
<210> 65 <211> 377 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(377) <223> n = A,T,C or G	
<400> 65 acaacaanaa ntcccttctt taggccactg atggaaacct ggaaccccct tttgatggca gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntccaa accgcacacc ccaaccctgg tctacccaca nttctggcta tgggctgtct ctgccactga acatcagggt tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg tgggggtgaa ctaccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag gggcgggagg agcatgt	60 120 180 240 300 360 377
<210> 66 <211> 305 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 66 acgcctttcc ctcagaattc agggaagaga ctgtcgcctg ccttcctccg ttgttgcgtg agaacccgtg tgccccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg aggaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tcctccacct tcctccactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt ttatatattt tttaataaga tgcactttat gtcattttt aataaagtct gaagaattac tgttt</pre>	60 120 180 240 300 305
<210> 67 <211> 385 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 67 actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga ggtcggacca gccacatctc atgtgcaaga ttgcccagca gacatcaggt ctgagagttc cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac catagtttct gtgctagtgg accgt</pre>	60 120 180 240 300 360 385
<210> 68 <211> 73 <212> DNA <213> Homo sapien	

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<400> 68
acttaaccag atatatttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                           60
                                                                           73
gtttttttaa tgg
      <210> 69
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (536)
      <223> n = A, T, C or G
      <400> 69
actagtocag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcagc
                                                                           60
                                                                         120
tocaqctttq tqctctqcct ctgaggagac catggcccag catctgagta ccctgctgct
                                                                         180
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                         240
                                                                         300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                         360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc
                                                                         420
agaactqcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                         480
                                                                         536
gaangtccct gggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 70
atgaccccta acaggggccc tctcagccct cctaatgacc tccggcctag ccatgtgatt
                                                                          60
tcacttccac tccataacqc tcctcatact aggcctacta accaacac taaccatata
                                                                         120
ccaatqatqq cqcqatqtaa cacqaqaaaq cacataccaa ggccaccaca caccacctqt
                                                                         180
ccaaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc
                                                                         240
                                                                         300
agggattttt ctgagccttt taccactcca gcctagcccc tacccccaa ctaggagggc
actggcccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
                                                                         360
ccqtattact cqcatcaqqa qtatcaatca cctqaqctca ccataqtcta ataqaaaaca
                                                                         420
                                                                         477
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (533)
      <223> n = A, T, C or G
      <400> 71
agagetatag gtacagtgtg ateteagett tgcaaacaca ttttetacat agatagtact
                                                                          60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
                                                                         120
tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                         180
                                                                         240
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt
taaataaaqq tttqtcatct ttaaaaaatac aqcaatatqt qacttttaa aaaaqctqtc
                                                                         300
aaataqqtqt qaccctacta ataattatta qaaatacatt taaaaaacatc qaqtacctca
                                                                         360
                                                                         420
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                         480
citegraatt ttggagtang aggtteette etcaattttg tatttttaaa aagtacatgg
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                         533
```

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<211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (511)
      <223> n = A, T, C or G
      <400> 72
                                                                      60
tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
                                                                     120
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga
                                                                     180
                                                                     240
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt
gaggttetet gtgtgeecac tggtttgaaa accgttetne aataatgata gaatagtaca
                                                                     300
cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcagaanac
                                                                     360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg
                                                                     420
atttctctcc attgcagcna naaacccgtt cttctaagca aacncaggtg atgatggcna
                                                                    480
                                                                     511
aaatacaccc cctcttgaag naccnggagg a
      <210> 73
      <211> 499
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (499)
      <223> n = A, T, C or G
      <400> 73
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac
                                                                      60
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
                                                                     120
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta
                                                                     180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                     240
                                                                     300
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
360
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc
                                                                     420
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact
                                                                     480
gtcctttcct aantaaaat
                                                                     499
      <210> 74
      <211> 537
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(537)
      <223> n = A, T, C or G
      <400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
                                                                      60
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
                                                                     120
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                     180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
                                                                     240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag
                                                                     300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                     360
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
                                                                     420
actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat
                                                                     480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt
                                                                     537
```

```
<210> 75
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (467)
      <223> n = A, T, C or G
      <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
tgcatattac acqtacctcc tcctqctcct caaqtaqtqt qqtctatttt qccatcatca
                                                                         120
                                                                         180
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                          240
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
tctagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                          300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                         360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                          420
                                                                          467
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(400)
      <223> n = A, T, C \text{ or } G
      <400> 76
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctcgcgctac
tetetette tggeetggag getatecage gtaetecaaa gatteaggtt taeteacgte atceageaga gaatggaaag teaaatttee tgaattgeta tgtgtetggg ttteatecat
                                                                         120
                                                                         180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag
                                                                          240
                                                                          300
acttgtcttt cagcaaggac tggtctttct atctcttgta ctacactgaa ttcaccccca
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                          360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                          400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
      <400> 77
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                           60
                                                                         120
ccagetgeec eggeggggga tgegaggete ggageaceet tgeeeggetg tgattgetge
caggeactgt teateteage ttttetgtee etttgeteee ggeaageget tetgetgaaa
                                                                          180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                         240
                                                                         248
aaaaaaa
      <210> 78
      <211> 201
      <212> DNA
      <213> Homo sapien
      <400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                           60
tcacccagac cccgccctgc ccgtgcccca cgctgctgct aacgacagta tgatgcttac
                                                                          120
tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttgttt ataaatgcct
                                                                         180
                                                                         201
gatttaaaaa aaaaaaaaaa a
```

```
<210> 79
      <211> 552
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (552)
      <223> n = A, T, C or G
      <400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt
                                                                        120
                                                                        180
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                        240
atgeaagtta gtaattacte agggttaact aaattacttt aatatgetgt tgaacctact
                                                                        300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga
                                                                        360
taatattcta tqttctaaaa qttqqqctat acataaanta tnaaqaaata tqqaatttta
                                                                        420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                        480
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                        540
aaaaaaaaa aa
                                                                        552
      <210> 80
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (476)
      <223> n = A, T, C or G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct
                                                                        120
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt
                                                                        180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta
                                                                        240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                        300
tettetaagt cetettecag ceteactttg agteeteett gggggttgat aggaantnte
                                                                        360
tcttqqcttt ctcaataaaa tctctatcca tctcatqttt aatttqqtac qcntaaaaat
                                                                        420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaaa aaaaaaaaaa aaaaaa
                                                                        476
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (232)
      <223> n = A, T, C or G
      <400> 81
tttttttttg tatgccntcn ctgtggngtt attgttgctg ccaccctgga ggagcccagt
                                                                         60
ttettetgta tetttettt etgggggate tteetggete tgeeecteea tteeeageet
                                                                       120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                        180
actcagtcag cgggaataag tcctaggggt qqqqgqtqtq qcaaqccqqc ct
                                                                        232
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
```

```
<220>
        <221> misc_feature
        <222> (1) ... (383)
        <223> n = A, T, C or G
        <400> 82
 aggogggago agaagotaaa gocaaagooo aagaagagtg goagtgooag cactggtgoo
                                                                               60
 agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg
                                                                              120
 gtgccagcet gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                              180
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt
                                                                              240
 qttaatcctq ccaqtctttc tcttcaaqcc agggtqcatc ctcagaaacc tactcaacac
                                                                              300
                                                                              360
 agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg
 ccatttcaaa aaaaaaaaaa aaa
                                                                              383
        <210> 83
        <211> 494
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc feature
        <222> (1) ... (494)
        <223> n = A, T, C or G
                                                                               60
. accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
 gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc
                                                                              120
                                                                              180
 ccatcctqct cqqttctccc caqatgacaa atactctcga caccgaatca ccatcaagaa
 acgetteaag gtgeteatga eccageaace gegeeetgte etetgagggt eettaaactg
                                                                              240
 atgtetttte tgccacetgt tacccetegg agactecgta accaaactet teggactgtg agecetgatg cetttttgee agecatacte tttggentee agtetetegt ggegattgat
                                                                              300
                                                                              360
 tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttganttttt
                                                                              420
 tttcncatat tttaaattac naccaqaata nttcaqaata aatgaattga aaaactctta
                                                                               480
                                                                              494
 aaaaaaaaa aaaa
        <210> 84
        <211> 380
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc feature
        <222> (1)...(380)
        <223> n = A, T, C or G
        <400> 84
 gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag
                                                                               60
                                                                              120
 gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                              180
                                                                              240
 gcacaccete etggggecca ggegggeace tgegtetece agtatgecaa etggetggtg
                                                                              300
 gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
 ccatqttcaq ttacacattc qqcaaaqtac agggcaacag cnatctctac tgggaaggcc
                                                                              360
                                                                              380
 agcgttnccg cctcatccgg
        <210> 85
        <211> 481
        <212> DNA
        <213> Homo sapien
        <221> misc_feature
```

```
<222> (1)...(481)
      <223> n = A, T, C or G
      <400> 85
gagttagete etecacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                         60
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca
                                                                       120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg
                                                                       180
tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga
                                                                       240
qtcqattctq catqtccaqc aqqaqqttqt accaqctctc tqacaqtqaq qtcaccaqcc
                                                                       300
ctatcatqcc nttqaacqtq ccqaaqaaca ccqaqccttq tqtqqqqqt qnaqtctcac
                                                                       360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
                                                                       420
aaaqaacacc tcctqqaaqt qctnqccgct cctcqtccnt tggtggnngc gcntnccttt
                                                                       480
                                                                       481
t
      <210> 86
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (472)
      <223> n = A, T, C or G
      <400> 86
                                                                         60
aacatcttcc tqtataatqc tqtqtaatat cqatccqatn ttqtctqctq agaattcatt
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt
                                                                       120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg
                                                                       180
                                                                       240
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt
                                                                       300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg
                                                                       360
ataintgage ggaagantag cetttetact teaceagaca caacteettt cataitggga
                                                                       420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                       472
      <210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc feature
      <222> (1) ... (413)
      <223> n = A, T, C \text{ or } G
      <400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                        60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                        120
                                                                       180
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                       240
tttattcqac atqaaqqaaa tttccaqatn acaacactna caaactctcc cttgactagg
                                                                       300
                                                                       360
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
                                                                       413
acagaaattg ggtngtatat tgaaananng catcattnaa acgtttttt ttt
     <210> 88
     <211> 448
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1) ... (448)
     <223> n = A,T,C or G
```

```
<400> 88
eqeagegggt cetetetate tageteeage etetegeetg ecceaeteee egegteeege
                                                                           60
gtectageen accatggeeg ggeecetgeg egeecegetg etectgetgg ceateetgge
                                                                          120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                          180
gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttgccg
                                                                          240
teggenanta caacaaacce geaacnactt ttacenagen egegetgeag gttgtgeege
                                                                          300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng tttaccagaa ccnagccaat tngaacaatt nccctccat aacagcccct tttaaaaagg
                                                                          360
                                                                          420
                                                                          448
gaancantcc tgntcttttc caaatttt
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (463)
      <223> n = A, T, C or G
      <400> 89
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca
                                                                           60
                                                                          120
gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc
agaggictag gictgcatat cagcagacag titgtccgtg tattitgtag ccttgaagtt
                                                                          180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc
                                                                          240
tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg
                                                                          300
                                                                          360
tttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn
                                                                          420
aattetetee ecatannaaa acceangeee ttggganaat ttgaaaaang gnteettenn
aattennana antteagntn teatacaaca naaenggane eec
                                                                          463
      <210> 90
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(400)
      <223> n = A, T, C or G
      <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
                                                                           60
cttccactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa tagaacaaat
                                                                          120
                                                                          180
tcttcaccag tcacatcttc taggaccttt ttggattcag ttagtataag ctcttccact
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattgct
                                                                          240
egttetetaa caatgteete teettgaagt atttggetga acaacceace tnaagteeet
                                                                          300
                                                                          360
ttgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctgcaa
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
                                                                          400
      <210> 91
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (480)
      <223> n = A, T, C or G
gageteggat ceaataatet ttgtetgagg geageacaea tatneagtge eatggnaact
```

```
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                        120
atgcctcttt gactaccgtg tgccagtgct ggtgattctc acacacctcc nnccgctctt
                                                                        180
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga
                                                                        240
gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt
                                                                        300
tgtcaatact aaccegetgg tttgcctcca tcacatttgt gatctgtagc tctggataca
                                                                        360
totoctgaca gtactgaaga actiottott ttgtttcaaa agcaactott ggtgootgtt
                                                                        420
ngatcaggtt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaaa
                                                                        480
      <210> 92
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (477)
      <223> n = A, T, C \text{ or } G
      <400> 92
atacagecea nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteaet
                                                                         60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt
                                                                        120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt
                                                                        180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc
                                                                        240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca
                                                                        300
                                                                        360
gaacetteeg cetgttetet ggegteacet geagetgetg cegetnacae teggeetegg
accageggae aaacggegtt gaacageege accteaegga tgeecantgt gtegegetee
                                                                        420
aggaacggcn ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg
                                                                        477
      <210> 93
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(377)
      <223> n = A, T, C or G
      <400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc
                                                                        60
                                                                        120
agtecgagea gecceagace getgeegeee gaagetaage etgeetetgg cetteeeete
cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn
                                                                        180
                                                                        240
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa
                                                                        300
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa
                                                                        360
ataaatatat tattaaa
                                                                        377
      <210> 94
      <211> 495
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(495)
      <223> n = A, T, C or G
      <400> 94
                                                                         60
ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc
egagetgang cagattteee acagtgacee cagageeetg ggetatagte tetgaceeet
                                                                        120
                                                                       180
ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgcccccc
                                                                       240
```

```
acgaggaana qgccctgant cctgggatca nacacccctt cacgtgtatc cccacacaaa
                                                                             300
tgcaagetea ceaaggteee eteteagtee ettecetaca ecetgaaegg neaetggeee
                                                                             360
acacccaccc agancancca cccgccatgg ggaatgtnct caaggaatcg cngggcaacg
                                                                             420
tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana
                                                                             480
aaaaaaana aaaaa
                                                                             495
      <210> 95
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (472)
      <223> n = A, T, C \text{ or } G
      <400> 95
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                              60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt tagctgttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctatttnact
                                                                             120
                                                                             180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt
                                                                             240
atgatgaaaa gcaatagata tatattettt tattatgttn aattatgatt gecattatta
                                                                             300
atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac
                                                                             360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata
                                                                             420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at
                                                                             472
      <210> 96
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (476)
      <223> n = A, T, C or G
      <400> 96
ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat
gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaagtctt
                                                                            120
ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt
                                                                            180
attetteaca gtagatgatg aaagagteet ceagtgtett gngcanaatg ttetagntat agetggatae ataengtggg agttetataa acteatacet eagtgggaet naaceaaaat
                                                                            240
                                                                            300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct
                                                                            360
qcaqqtactc ctccaqaaaa acnqacaqqq caqqcttqca tqaaaaaqtn acatctqcqt
                                                                            420
tacaaagtet atetteetea nangtetgtn aaggaacaat ttaatettet agettt
                                                                            476
      <210> 97
      <211> 479
      <212> DNA
      <213> Homo sapien
      <221> misc feature
      <222> (1) ... (479)
      <223> n = A, T, C or G
      <400> 97
actettteta atgetgatat gatettgagt ataagaatge atatgteact agaatggata
                                                                             60
aaataatgct gcaaacttaa tgttcttatg caaaatggaa cgctaatgaa acacagctta
                                                                            120
                                                                            180
caatcgcaaa tcaaaactca caagtgctca tctgttgtag atttagtgta ataagactta
                                                                            240
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PCT/US00/27464

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		Glu	Asp	Met	Asp 85		Ala	Leu	Met	Glu 90		Ser	Asn	Cys	Ser 95		
	Glu	Pro	Gly	Phe 100		Ala	His	Pro	Pro 105		Ala	Gln	Ala	Gly 110		Cys	
	Val	Ser	Gln	Tyr	Ala	Asn	Trp	Leu		Val	Leu	Leu	Leu		Ile	Phe	

Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys 145 150 155 160 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln 190 -Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp 225 230 235 240 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp <210> 113 <211> 553 <212> PRT <213> Homo sapien <400> 113 Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala Gln Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Glu Val Gly Val
35 40 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly 50 60 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

WO 01/25272

40

PCT/US00/27464

Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu 245 250 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg 260 265 270 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe 275 280 285 275 280 285 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val 295 300 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly 305 310 315 320 310 315 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu 325 330 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg 340 345 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala 360 365 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu 370 375 380 375 380 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala 385 390 395 400 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly
405
410
415 405 410 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu 420 425 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala 435 440 445 . Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser 455 460 Ala Cys Asp Val Ser Val Arg Val Val Gly Glu Pro Thr Glu Ala 470 475 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp 495 490 495 485 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser 505 510 500 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala 520 525 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp 535 Lys Ser Asp Leu Ala Lys Tyr Ser Ala 550 545

<210> 114

<211> 241

<212> PRT

<213> Homo sapien

<400> 114

Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu 10 Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val 25 20 Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser 40 45 Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly 55 Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr 75 Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile 95 85 90 Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr 100 105 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys

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120
                                                125
        115
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
                        135
                                            140
   130
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
                                        155
145
                    150
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                                    170
                                                        175
                165
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
                                185
                                                     190
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
                            200
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
                        215
                                            220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
                                        235
225
                    230
Gln
      <210> 115
      <211> 366
      <212> DNA
      <213> Homo sapien
      <400> 115
                                                                        60
qctctttctc tcccctcctc tgaatttaat tctttcaact tgcaatttgc aaggattaca
                                                                        120
catttcactg tgatgtatat tgtgttgcaa aaaaaaaaa gtgtctttgt ttaaaattac
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                        180
                                                                        240
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                        300
tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaat tagtttgggt
                                                                        360
tctctacatg cataacaaac cctgctccaa tctgtcacat aaaagtctgt gacttgaagt
                                                                        366
ttagtc
      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(282)
      <223> n = A, T, C or G
      <400> 116
acaaagatga accatttcct atattatagc aaaattaaaa tctacccgta ttctaatatt
                                                                        60
                                                                        120
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa
                                                                        180
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt
                                                                        240
tcaatcinga actatciana tcacagacat tictaticci ti
                                                                        282
      <210> 117
      <211> 305
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (305)
      <223> n = A, T, C or G
      <400> 117
                                                                        60
acacatgtcg cttcactgcc ttcttagatg cttctggtca acatanagga acagggacca
                                                                        120
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa
```

```
aataaqqcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                        180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt
                                                                        240
                                                                        300
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
                                                                        305
tgggt
      <210> 118
      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(71)
      <223> n = A, T, C or G
      <400> 118
accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa
                                                                         60
                                                                         71
aantcctggg t
      <210> 119
      <211> 212
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (212)
      <223> n = A, T, C or G
      <400> 119
                                                                         60
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gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac
                                                                        120
agtaagctgg cccttctaat aaaagaaaat tgaaaggttt ctcactaanc ggaattaant
                                                                        180
                                                                        212
aatggantca aganactccc aggcctcagc gt
      <210> 120
      <211> 90
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (90)
      <223> n = A, T, C or G
      <400> 120
actegttgca nateagggge cececagagt cacegttgca ggagteette tggtettgee
                                                                         60
                                                                         90
ctccgccggc gcagaacatg ctggggtggt
      <210> 121
      <211> 218
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (218)
      <223> n = A, T, C or G
      <400> 121
                                                                         60
tqtancqtqa anacqacaqa naqqqttqtc aaaaatqqaq aanccttgaa qtcattttga
                                                                        120
gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag
```

atatncangt agcatanact				ggaattcctt	tacgatngcc	180 218
<210> <211> <212> <213>	171	en				
<400>						
taggggtgta catttgttag caccaccccg	ctcatggaac	aggaagtcgg	atggtggggc	atcttcagtg	ctgcatgagt	60 120 171
<210> <211> <212> <213>	76	en				
<222>	misc_featu (1)(76)	•			·	
<223>	n = A, T, C	or G			•	
<400> tgtagcgtga ttatcaanta	agacnacaga	atggtgtgtg	ctgtgctatc	caggaacaca	tttattatca	60 76
<210> <211> <212> <213>	131	en				
	_			•		
<400> acctttcccc caatgtgctg ttaagatttg	aaggccaatg ggtcatatgg					60 120 131
<210> <211> <212> <213>	432	en				
<400>						
actttatcta cttgaaaaag ctacagtctg ttgcctcacc ctcttgaagt catggtgggg caggaaacat ctctttgctt	aggtgatagc catttggcag aaacaaaagt atcagtcact gtcttgcatc cagaaccact	tcttcagagg aaatgaagat gaaacaactg tttgagaatg tgtaagaatg	acttgtgact gaatttggat agagaaaatt tttcttagtt gaattgattt	tttgctcaga taaatgagga ttcaggaaaa actgcatact tgcttttgca	tgctgaagaa tgctgaagat aagacagtgg tcatggatcc agaatctcag	60 120 180 240 300 360 420 432
<210> <211> <212> <213>	112	en				
<400> acacaacttg agtaagaatg	aatagtaaaa					60 112
<210>	127					

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<211> 54
      <212> DNA
      <213> Homo sapien
      <400> 127
accacqaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag
                                                                            54
      <210> 128
      <211> 323
      <212> DNA
      <213> Homo sapien
      <400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc
                                                                            60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca
                                                                           120
ttetetetga agtetaggtt acceattitg gggacceatt ataggeaata aacacagtte ceaaageatt tggacagttt ettgttgtgt tttagaatgg tttteetttt tettageett
                                                                           180
                                                                           240
ttectqcaaa aggeteacte agteectige ttgeteagtg gactgggete eccagggeet
                                                                           300
aggetgeett etttteeatg tee
                                                                           323
      <210> 129
      <211> 192
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (192)
      <223> n = A, T, C or G
      <400> 129
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatac
                                                                            60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc
                                                                           120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
                                                                           180
                                                                           192
gataaacaaa gt
      <210> 130
<211> 362
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (362)
      <223> n = A, T, C or G
      <400> 130
ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca
                                                                            60
tataatqacq caacaaaaq qtqctqttta qtcctatqqt tcaqtttatq cccctqacaa
                                                                           120
qtttccattq tqttttgccq atcttctggc taatcqtggt atcctccatq ttattagtaa
                                                                           180
ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata
                                                                           240
                                                                           300
cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat
                                                                           360
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatctta aaaagtaatg
                                                                           362
gg
      <210> 131
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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45
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<222> (1)...(332)
      <223> n = A, T, C or G
ctttttqaaa qatcqtqtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca
                                                                            60
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga
                                                                           120
gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa
                                                                           180
                                                                           240
cttccatctq ttatcactqg agaaagccca gactccccan gacnggtacg gattgtgggc
                                                                           300
atanaaggat tgggtgaagc tggcgttgtg gt
                                                                           332
      <210> 132
      <211> 322
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (322)
      \langle 223 \rangle n = A, T, C or G
      <400> 132
acttttgcca ttttgtatat ataaacaatc ttgggacatt ctcctgaaaa ctaggtgtcc
                                                                            60
aqtqqctaaq aqaactcqat ttcaaqcaat tctgaaaqga aaaccaqcat gacacagaat
                                                                           120
                                                                           180
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg
                                                                           240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
                                                                           300
                                                                           322
gtaacaatct acaattggtc ca
      <210> 133
      <211> 278
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (278)
      <223> n = A, T, C or G
      <400> 133
acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt
                                                                            60
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
                                                                           120
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg
                                                                           180
                                                                           240
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
cccacgaaac actaataaaa accacagaga ccagcctg
                                                                           278
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (121)
      <223> n = A, T, C or G
      <400> 134
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                            60
tgattctctg aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg
                                                                           120
                                                                           121
```

<210> 135

PCT/US00/27464 WO 01/25272

46

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<211> 350
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (350)
      <223> n = A, T, C or G
      <400> 135
                                                                        60
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc
                                                                       120
aaacttqata cttttqttct aagtaggaac tagtatacag tncctaggan tggtactcca
                                                                       180
                                                                       240
gggtgcccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct
                                                                        300
ccacctcaat caagecetgg gecatgetae etgeaattgg etgaacaaac gtttgetgag
                                                                       350
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt
      <210> 136
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(399)
      <223> n = A, T, C or G
      <400> 136
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt
                                                                       120
gctqtqattq tatccqaata ntcctcqtqa qaaaaqataa tgaqatgacq tqaqcaqcct
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                       180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag
                                                                       240
aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                       300
                                                                       360
teccaggaac eegggcaaag gecateecca eetacageca geatgeecae tggegtgatg
ggtgcagang gatgaagcag ccagntgttc tgctgtggt
                                                                       399
      <210> 137
      <211> 165
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(165)
      <223> n = A, T, C or G
      <400> 137
actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt
                                                                        60
                                                                       120
qqaqqaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga
                                                                       165
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
      <210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(338)
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<223> n = A, T, C or G

<400> 138

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actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc
                                                                           60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                          120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                          180
                                                                          240
cangceteag gaageeteaa gtteeattea getttgeeae tgtacattee ecatntttaa
                                                                          300
                                                                          338
aaaaactgat gcctttttt ttttttttt taaaattc
      <210> 139
      <211> 382
      <212> DNA
      <213> Homo sapien
      <400> 139
gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa
                                                                           60
                                                                          120
qaaaqqqact togaqtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga
atteaaacag acctegteat teetggtgtg ageetggteg geteacegee tateatetge
                                                                          180
                                                                          240
atttqcctta ctcaqqtqct accqqactct ggcccctgat gtctgtagtt tcacaggatg
cettatttqt ettetacace ccacagggce cectacttet teggatgtgt ttttaataat
                                                                          300
gtcagctatg tgccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagtg
                                                                          360
                                                                          382
gcctggaact tgtttaaagt gt
      <210> 140
      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature -
      <222> (1)...(200)
      <223> n = A, T, C or G
      <400> 140
                                                                           60
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                          120
acttttcatt taacancttt tgttaagtgt caggctgcac tttgctccat anaattattg
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                          180
                                                                          200
atattcagca taaaggagaa
      <210> 141
      <211> 335
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (335)
      <223> n = A, T, C or G
      <400> 141
                                                                           60
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg
                                                                          120
qqqtqctqac taaacttcaa qtcacagact tttatqtqac agattqqagc aggqtttqtt
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga
                                                                          180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg
                                                                          240
                                                                          300
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg
attcacaaac caagtaattt taaacaaaga cactt
                                                                          335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <221> misc_feature
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<222> (1)...(459)
      <223> n = A, T, C or G
      <400> 142
accappttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta
                                                                            60
                                                                           120
gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat
ctgatggaga aaacactgag tittgacaaa tottattta ticagatagc agtctgatca
                                                                           180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc
                                                                           240
ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca
                                                                           300
tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga
                                                                           360
agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct
                                                                           420
cagcangggt gggaggaacc agctcaacct tggcgtant
                                                                           459
      <210> 143
      <211> 140
      <212> DNA
      <213> Homo sapien
      <400> 143
                                                                            60
acattteett ecaccaagte aggacteetg gettetgtgg gagttettat cacetgaggg
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag
                                                                           120
accatccgac ttccctgtgt
                                                                           140
      <210> 144
      <211> 164
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(164)
      <223> n = A, T, C or G
      <400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct
                                                                            60
atctatacca ctctcccttc tqaaaacaan aatcactanc caatcactta tacaaatttg
                                                                           120
aggcaattaa tocatatttg tittoaataa ggaaaaaaag atgt
                                                                           164
      <210> 145
      <211> 303
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (303)
      <223> n = A, T, C or G
      <400> 145
                                                                            60
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa
actggagggt atttataccc aattatecca tteattaaca tgeceteete eteaggetat
                                                                           120
qcaqqacaqc tatcataaqt cqqcccaqqc atccaqatac taccatttqt ataaacttca
                                                                           180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat
                                                                           240
                                                                           300
caa
                                                                           303
      <210> 146
<211> 327
      <212> DNA
      <213> Homo sapien
      <220>
```

```
<221> misc_feature
      <222> (1) ... (327)
      <223> n = A, T, C \text{ or } G
      <400> 146
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac
                                                                           60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct
                                                                          120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                           180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                          240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg
                                                                           300
taggggtgag ctgtgtgact ctatggt
                                                                           327
      <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(173)
      <223> n = A, T, C or G
      <400> 147
acattqtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg
                                                                           60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                           120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                          173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (477)
      <223> n = A, T, C or G
      <400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct
                                                                           60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg
                                                                          120
                                                                          180
gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac
                                                                          240
nccancecae etcacegace ceatectett acacagetae etcettgete tetaacecea
                                                                          300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
                                                                          360
caccactggt aagcettete cagccaacac acacacacac acacncacac acacacatat
                                                                          420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg
                                                                          477
      <210> 149
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac
                                                                           60
taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                          120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                          180
tttcaggcag agggaacagc agtgaaa
                                                                          207
      <210> 150
      <211> 111
      <212> DNA -
      <213> Homo sapien
```

50

```
<220>
      <221> misc_feature
      <222> (1)...(111)
      <223> n = A, T, C or G
      <400> 150
accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg
                                                                        60
                                                                       111
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t
      <210> 151
      <211> 196
      <212> DNA
      <213> Homo sapien
      <400> 151
agcgcggcag gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac
                                                                        60
                                                                        120
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacgag
                                                                       180
                                                                       196
gtgcatccgg ctcagt
      <210> 152
      <211> 132
      <212> DNA
    / <213> Homo sapien
      <400> 152
                                                                        60
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga atagaaccag
                                                                       120
                                                                       132
gagggagttt gt
      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(285)
      <223> n = A, T, C or G
      <400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag
                                                                        60
                                                                       120
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatcaacac
                                                                       180
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca
                                                                       240
                                                                       285
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt
      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien
      <400> 154
                                                                        60
accacagtee tgttgggeca gggetteatg accetttetg tgaaaageca tattateace
                                                                       120
accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac
                                                                       180
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg
                                                                       240
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg
                                                                       300
agtiticacaa attotogggc cacctogtca ttgctcctct gaaataaaat coggagaatg
                                                                       333
gtcaggcctg tctcatccat atggatcttc cgg
```

<210> 155

<212> DNA

WO 01/25272 PCT/US00/27464

```
<211> 308
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(308)
      <223> n = A, T, C or G
      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg
qaaaqtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                        120
ttgaatcacg gtgcatacaa acteteetge etgeteetee tgggeeceag eeceageece
                                                                        180
atcacagete actgetetgt teatecagge ceageatgta gtggetgatt ettettgget
                                                                        240
                                                                        300
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcatgctg
                                                                        308
gccctggt
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta
                                                                         60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                        120
                                                                        180
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctccttgcct cattctatgt
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                        240
aaaaccagat qtctatcctt aagattttca aatagaaaac aaattaacag actat
                                                                        295
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
                                                                         60
qaaqaqcaaa acaaattctq tcatqtaatc tctatcttqq gtcgtgggta tatctgtccc
                                                                        120
                                                                        126
cttagt
      <210> 158
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (442)
      <223> n = A, T, C \text{ or } G
      <400> 158
acceactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg
                                                                         60
aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt
                                                                        120
qcctqqqtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt
                                                                        180
                                                                        240
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtggtg
                                                                        300
                                                                        360
ccaaccctqt tttcccaqtc cacqtaqaca qattcacagt qcqqaattct qqaaqctgqa
                                                                        420
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg
                                                                        442
tgttcattct ctgatgtcct gt
      <210> 159
      <211> 498
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (498)
      <223> n = A, T, C or G
      <400> 159
                                                                        60
acttccaqqt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc
tccaacaaqa actqaqqttq caqaqcqqqt agggaagagt gctqttccag ttgcacctgg
                                                                       120
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag
                                                                       180
gtgtgttgtt gganttgagc tegggegget gtggtaggtt gtgggetett caacagggge
                                                                       240
                                                                       300
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt
antanattet teetgaagge cagegettgt ggagetggea ngggteantg ttgtgtgtaa
                                                                       360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn
                                                                       420
                                                                       480
tcaggtaana atgtggtttc agtgtccctg ggengctgtg gaaggttgta nattgtcacc
                                                                       498
aagggaataa gctgtggt
      <210> 160
      <211> 380
      <212> DNA
     <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (380)
      <223> n = A,T,C or G
      <400> 160
acctgcatcc agettccctg ccaaactcac aaggagacat caacctctag acagggaaac
                                                                        60
agetteagga taetteeagg agacagagee accageagea aaacaaatat teecatgeet
                                                                       120
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc
                                                                       180
cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc
                                                                       240
ccaccettac etecatetea cacacttgag etttecacte tgtataatte taacateetg
                                                                       300
                                                                       360
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa
                                                                       380
cttgtagaat gaagcctgga
      <210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
actccacatc ccctctgagc aggcggttgt cgttcaaggt gtatttggcc ttgcctgtca
                                                                        60
cactqtccac tqqcccctta tccacttggt gcttaatccc tcgaaagagc atgt
                                                                       114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
                                                                        60
actttctqaa tcqaatcaaa tqatacttag tgtagtttta atatcctcat atatatcaaa
                                                                       120
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                       177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
```

```
<221> misc_feature
      <222> (1) ... (137)
      <223> n = A, T, C or G
      <400> 163
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac
                                                                        60
canagaagge agetacgget actectacat cetggegtgg gtggeetteg cetgeacett
                                                                       120
catcagcggc atgatgt
                                                                        137
      <210> 164
      <211> 469
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (469)
      <223> n = A, T, C or G
      <400> 164
                                                                        60
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                       120
tgcatggatc tcaaaggaaa caaacacca ataaactcgg agtggcagac tgacaactgt
                                                                       180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg
                                                                        240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                       300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                       360
totagtagge acagggetee caggecagge eteattetee tetggeetet aatagteaat
                                                                        420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt
                                                                        469
      <210> 165
     · <211> 195
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (195)
      <223> n = A, T, C or G
      <400> 165
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
                                                                       120
atcogctgtc atcoactatt ccttggctag agtaaaaatt attcttatag cccatgtccc
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
                                                                       180
tcctctgaga tgagt
                                                                       195
      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (383)
      <223> n = A, T, C or G
      <400> 166
                                                                        60
acatettagt agtgtggcac atcaggggc catcagggtc acagtcactc atagcetege
                                                                       120
cqaqqtcqqa qtccacacca ccqqtqtaqq tqtqctcaat cttqqqcttq gcgcccacct
                                                                       180
tiggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg
                                                                       240
                                                                       300
gatgccaacc tcgtctangg tccgtgggaa gctggtgtcc acntcaccta caacctgggc
gangatetta taaagagget eenagataaa eteeacgaaa ettetetggg agetgetagt
                                                                       360
```

```
nggggccttt ttggtgaact ttc
                                                                           383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <221> misc feature
      <222> (1) ... (247)
      <223> n = A, T, C or G
      <400> 167
acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat
                                                                            60
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc
                                                                           120
tatanccata cacagagcca actoteagge caaggenatg gttggggeag anccagagae
                                                                           180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                           240
tgangtc
                                                                           247
      <210> 168
      <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (273)
      <223> n = A, T, C or G
      <400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa
                                                                            60
aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg
                                                                           120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                           180
aattoccaac ttoottgcca caagettocc aggetttotc cootggaaaa ctocagettg
                                                                           240
agtcccagat acactcatgg gctgccctgg gca
                                                                           273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (431)
      <223> n = A, T, C or G
      <400> 169
acagcettgg cttccccaaa ctccacagte teagtgeaga aagateatet tecageagte
                                                                            60
ageteagace agggteaaag gatgtgacat caacagttic tggtttcaga acaggttcta
                                                                           120
ctactgtcaa atgacccccc atacticctc aaaggctgtg gtaagtttig cacaggtgag
                                                                           180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac
                                                                           240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc
                                                                           300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc
                                                                           360
                                                                           420
tcgaacactg a
                                                                           431
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
```

```
<221> misc_feature
      <222> (1) ... (266)
      <223> n = A, T, C or G
      <400> 170
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc
                                                                           60
tcaaggaget etgeaggeat tttgccaane etetecanag canagggage aacetacaet
                                                                          120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                          180
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                          240
                                                                          266
tcaaagctag gggtctggca ggtgga
      <210> 171
      <211> 1248
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (1248)
      <223> n = A, T, C or G
      <400> 171
qqcaqccaaa tcataaacgq cgaggactqc agcccgcact cgcaqccctg gcaggcggca
                                                                           60
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg
                                                                          120
                                                                          180
teageegeae actgttteea gaagtgagtg cagageteet acaccategg getgggeetg
cacagtettg aggeegacea agageeaggg ageeagatgg tggaggeeag ceteteegta eggeacecag agtacaacag accettgete getaacgace teatgeteat caagttggae
                                                                          240
                                                                          300
quatecqtqt ecquqtetqu caccatecqq agcateagca ttgettegca qtgecetaec
                                                                          360
                                                                          420
geggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc
gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctëtatgac
                                                                          480
ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc aacggtgact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc
                                                                          540
                                                                          600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                          660
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
                                                                          720
                                                                          780
attgacccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct
ccctcaggcc caggagtcca ggcccccagc ccctcctccc tcaaaccaag ggtacagatc
                                                                          840
cccagcccct cctccctcag acccaggagt ccagaccccc cagcccctcc tccctcagac
                                                                          900
ccaggagtcc agcccctcct ccctcagacc caggagtcca gaccccccag cccctcctcc
                                                                          960
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagccc
                                                                        1020
ccaaccente attecceaga cccagaggte caggteccag eccetentee etcagaccea
                                                                        1080
geggtecaat gecaectaga etntecetgt acacagtgce ecettgtgge aegttgaece
                                                                        1140
aaccttacca gttggttttt cattttingt coctttcccc tagatccaga aataaagttt
                                                                        1200
1248
      <210> 172
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
      <223> Xaa = Any Amino Acid
      <400> 172
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
                  5
                                     10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
                                 25
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
                            40
                                                  45
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
```

```
55
 Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
                     70
                                          75
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
                                      90
 Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
                                  105
             100
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
                              120
                                                   125
         115
 Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                                               140
     130
                          135
 Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
       <210> 173
       <211> 1265
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (1265)
       <223> n = A, T, C or G
       <400> 173
 ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
                                                                           60
                                                                          120
 togggogtee tggtgeatee geagtgggtg etgteageeg cacactgttt ceagaactee
 tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg
                                                                           180
 qtqqaqqcca gcctctccqt acggcaccca gagtacaaca gacccttgct cgctaacgac
                                                                           240
 ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc
                                                                           300
                                                                           360
 attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg gggtctgctg
 gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga
                                                                           420
                                                                           480
 acqtqtcqqt qqtqtctqaq qaqqtctqca qtaagctcta tgacccgctg taccacccca
                                                                           540
                                                                           600
 qcatqttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg
                                                                           660
 ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg
 gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
                                                                           720
 aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                           780
 atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag
                                                                           840
                                                                           900
 tecaggeee cagecetee teceteaaac caagggtaca gateeecage eceteetee
 tcagacccag gagtccagac cccccagccc ctcctccctc agacccagga gtccagcccc
                                                                           960
 tcctccntca gacccaggag tccagacccc ccagcccctc ctccctcaga cccaggggtt
                                                                         1020
 gaggececca accectecte etteagagte agaggtecaa gececeaace ectegitece
                                                                         1080
 cagacccaga ggtnnaggtc ccagcccctc ttccntcaga cccagnggtc caatgccacc
                                                                         1140
                                                                         1200
 tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttggt
                                                                         1260
 ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa
                                                                         1265
 aaaaa
       <210> 174
       <211> 1459
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(1459)
       <223> n = A,T,C \cdot or G
       <400> 174
                                                                           60
 ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc
                                                                          120
 tqcacaqtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg
                                                                           180
```

tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg

```
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcccta
                                                                            240
ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg
                                                                            300
gtgtgtgtct gccctcttca aggaggtcct ctgcccagtc gcgggggctg acccagagct
                                                                            360
ctgcqtccca qqcaqaatqc ctaccqtqct gcagtgcgtg aacgtgtcgg tggtgtctga
                                                                            420
ngaggtetge antaagetet atgacceget gtaccaccec ancatgttet gegeeggegg
                                                                            480
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact
                                                                            540
                                                                            600
cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag
                                                                            660
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc
                                                                            720
                                                                            780
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt
gacctccacc caatagaaaa tectettata acttttgact ecccaaaaac etgactagaa
                                                                            840
atagectact gttgaegggg agecttacea ataacataaa tagtegattt atgeataegt
                                                                            900
                                                                            960
tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc
gtctgtgaat ttttttaaat tgttgcaact ctcctaaaat ttttctgatg tgtttattga
                                                                           1020
aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa
                                                                           1080
                                                                           1140
aaatcaagac tctacaaaga ggctgggcag ggtggctcat gcctgtaatc ccagcacttt
                                                                           1200
qqqaqqcqaq qcaqqcaqat cacttqaqqt aaqqaqttca aqaccagcct qqccaaaatq
                                                                           1260
gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt
                                                                           1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt
                                                                           1380
qaaqtqaqtt qaqatcacac cactatactc caqctggggc aacagagtaa gactctgtct
                                                                           1440
                                                                           1459
caaaaaaaaa aaaaaaaaa
      <210> 175
      <211> 1167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (1167)
      <223> n = A, T, C or G
      <400> 175
gcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgtcctg
                                                                             60
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg
                                                                            120
                                                                            180
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc
                                                                            240
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag
                                                                            300
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga
                                                                            360
                                                                            420
atgcctaccg tgctgcactg cgtgaacgtg tcggtggtgt ctgaggangt ctgcagtaag
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt
                                                                            480
                                                                            540
gtgtctttcg gaaaagcccc gtgtggccaa cttggcgtgc caggtgtcta caccaacctc
                                                                            600
tqcaaattca ctqaqtqqat aqaqaaaacc qtccaqncca gttaactctg gggactggga
                                                                            660
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca
                                                                            720
gccctcctc cctcaggccc aggagtccag gccccagcc cctcctcct caaaccaagg gtacagatcc ccagccctc ctccctcaga cccaggagtc cagaccccc agcccctcnt
                                                                            780
                                                                            840
contragace caggagtera geoecteete entragacge aggagterag accececage
                                                                           900
                                                                            960
cententeeg teagaceeag gggtgeagge ecceaacee tenteentea gagteagagg
                                                                           1020
tecaageeee caaceeeteg tteeceagae ceagaggtne aggteecage cecteeteee
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc ccttgtggca
                                                                          1080
ngttgaccca accttaccag ttggtttttc attttttgtc cctttcccct agatccagaa
                                                                          1140
                                                                          1167
ataaagtnta agagaagcgc aaaaaaa
      <210> 176
      <211> 205
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
```

58

<222> (1)...(205) <223> Xaa = Any Amino Acid <400> 176 Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp 1 10 Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu 20 25 30 Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val . 40 Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu 55 Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser 70 Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly 85 90 Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met 100 105 110 Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val 120 125 Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala 135 140 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly 150 155 Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys 165 170 175 Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys 180 185 Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser 195 200 <210> 177 <211> 1119 <212> DNA <213> Homo sapien <400> 177 60 gcgcactcgc agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc 120 atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag 180 gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg 240 ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct 300 tegeagtgee etacegeggg gaactettge etegtttetg getggggtet getggegaac 360 gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc 420 caaccetgge agggttgtac cattteggea actteeagtg caaggacgte etgetgeate 480 540 ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600 actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc 660 cagttatect caetgaattg agattteetg etteagtgte agceatteee acataattte 720 780 tgacctacag aggtgaggga tcatatagct cttcaaggat gctggtactc ccctcacaaa ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca 840 ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900 ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960 accaecteag gacteetgga ttetetgeet agttgagete etgeatgetg ceteettggg 1020 1080 gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc

<210> 178

<211> 164

<212> PRT

<213> Homo sapien

ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa

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<220>
      <221> VARIANT
      <222> (1)...(164)
      <223> Xaa = Any Amino Acid
      <400> 178
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
1
                                     10
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
            20
                                 25
                                                     30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                             40
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
                        55
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                    70
                                         75
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85
                                     90
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
                                 105
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
                            120
                                                 125
        115
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
                        135
                                             140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
Pro Gly Thr Leu
      <210> 179
      <211> 250
      <212> DNA
      <213> Homo sapien
      <400> 179
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                         60
ccaqctqccc ccqqccqqqq qatqcqaqqc tcqqaqcacc cttqcccqqc tqtgattqct
                                                                        120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgctga
                                                                        180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa
                                                                        240
aaaaaaaaa
                                                                        250
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                         60
teacceagae ecegeceetg ecegtgeece aegetgetge taacgacagt atgatgetta
                                                                        120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
                                                                        180
                                                                        202
tgatttaaaa aaaaaaaaa aa
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(558)
      <223> n = A, T, C \text{ or } G
```

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<400> 181
tccytttqkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcyngg
                                                                          60
aatgtttagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct
                                                                          120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                         180
qqtaqtqtqa taqtataaqt atctaagtqc agatqaaaqt gtgttatata tatccattca
                                                                         240
aaattatqca aqttaqtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                         300
                                                                         360
ctactctqtt ccttqqctaq aaaaaattat aaacaggact ttqttaqttt qggaaqccaa
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt
                                                                         420
                                                                          480
aaaaycaqtt ttqqtwaata yqtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                         540
                                                                         558
caaaaaaaa aaaaaaaa
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (479)
      <223> n = A, T, C or G
      <400> 182
                                                                          60
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc
                                                                         120
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtg gcacccctgg
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg
                                                                         180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                         240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca
                                                                         300
tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
                                                                         360
                                                                         420
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaaa
                                                                         479
      <210> 183
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 183
aggeggage agaagetaaa gecaaageee aagaagagtg geagtgeeag caetggtgee
                                                                          60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                         120
                                                                         180
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat
                                                                          240
                                                                         300
tgttaateet gecagtettt etetteaage cagggtgeat eeteagaaac etaeteaaca
cagcacteta ggcagecact atcaatcaat tgaagttgac actetgeatt aratetattt
                                                                         360
                                                                         384
qccatttcaa aaaaaaaaaa aaaa
      <210> 184
      <211> 496
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (496)
      <223> n = A, T, C \text{ or } G
      <400> 184
                                                                          60
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agggagatcg agtctatacg ctgaagaaat ttgacccgat gggacaacag acctgctcag
                                                                         120
                                                                         180
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga
aacgetteaa ggtgeteatg acceageaac egegeeetgt cetetgaggg teeettaaac
                                                                         240
tgatgtettt tetgecacet gttaccete ggagaeteeg taaccaaact etteggaetg
                                                                         300
```

```
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                                360
attatgcttg tgtgaggcaa tcatggtggc atcacccata aagggaacac atttgacttt
                                                                                420
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                                480
                                                                                496
taaaaaaaa aaaaaa
       <210> 185
       <211> 384
       <212> DNA
       <213> Homo sapien
       <400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
                                                                                 60
caaqtatcyt qcqcsqcqtc ttctaccqtc cctacctqca qatcttcqqq caqattcccc
                                                                                120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct
                                                                                180
                                                                                240
gggcacaccc tcctggggcc caggcgggca cctgcgtctc ccagtatgcc aactggctgg
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                                300
                                                                                360
gcgcagcgtt accgcctcat ccgg
                                                                                384
       <210> 186
       <211> 577
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
      \langle 222 \rangle (1)...(577)
\langle 223 \rangle n = A,T,C or G
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc
                                                                                 60
tnccatcgtc atactgtagg tttgccacca cytcctggca tcttggggcg gcntaatatt
                                                                                120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc tcggtgtgaa aggatctccc agaaggagtg ctcgatcttc cccacacttt tgatgacttt
                                                                                180
                                                                                240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                                300
cagccctatc atgccgttga mcgtgccgaa garcaccgag ccttgtgtgg gggkkgaagt
                                                                                360
ctcacccaga ttctgcatta ccagagagcc gtggcaaaag acattgacaa actcgcccag
                                                                                420
gtggaaaaag amcamcteet ggargtgetn geegeteete gtemgttggt ggeagegetw teettttgae acacaaacaa gttaaaggea tttteageee ecagaaantt gteateatee
                                                                                480
                                                                                540
aagatntcgc acagcactna tccagttggg attaaat
                                                                                577
       <210> 187
      <211> 534
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(534)
      \langle 223 \rangle n = A,T,C or G
      <400> 187
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw
                                                                                 60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                                120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta
                                                                                180
tgccctattc acacetgtta aaagggcgct aagcattttt gattcaacat ctttttttt
                                                                                240
gacacaagte egaaaaage aaaagtaaac agttatyaat ttgttageea atteaettte
                                                                                300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                                360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg
                                                                                420
ggatgitnac naaagtwatg tototwacag atgggatgot tttgtggcaa ttctgttctg
                                                                                480
aggatetece agtttattta ceaettgeae aagaaggegt tttetteete agge
                                                                                534
```

```
<210> 188
      <211> 761
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(761)
      <223> n = A, T, C or G
      <400> 188
aqaaaccaqt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                             60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                            120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                            180
                                                                            240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                            300
qqqqacaaaq aaaaqcaaaa ctqamcataa raaacaatwa cctqqtqaga arttqcataa
                                                                            360
acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                            420
gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgtttttt tatnataaaa
                                                                            480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
                                                                            540
                                                                            600
atgettaatt cacaaatget aattteatta taaatgtttg etaaaataca etttgaacta
                                                                            660
ttittctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac
                                                                            720
gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                            761
      <210> 189
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(482)
      <223> n = A, T, C or G
      <400> 189
ttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccgca
                                                                             60
                                                                            120
caccggggct atnagaagca agaaggaagg agggagggca cagcccttg ctgagcaaca
aagecgectg etgeettete tgtetgtete etggtgeagg cacatgggga gacetteece
                                                                            180
                                                                            240
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                            300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
                                                                            360
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg
                                                                            420
gttcggcca gctccncqtc caaaaantat tcacccnnct ccnaattgct tgcnggnccc
                                                                            480
                                                                            482
      <210> 190
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (471)
      <223> n = A, T, C or G
      <400> 190
                                                                            60
tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg
                                                                            120
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca
                                                                           180
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag
                                                                           240
cgcttttgac atacaatgca caaaaaaaa agggggggg gaccacatgg attaaaattt
                                                                           300
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
```

```
tqaaaaattt catqtatqca atccaaccaa agaacttnat tqqtqatcat gantnctcta
                                                                         360
ctacatenac cttgatcatt gccaggaacn aaaagttnaa ancacnengt acaaaaanaa
                                                                         420
                                                                         471
tctgtaattn anttcaacct ccgtacngaa aaatnttnnt tatacactcc c
      <210> 191
      <211> 402
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (402)
      <223> n = A, T, C or G
gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct
                                                                          60
                                                                         120
gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa
attetteace agteacatet tetaggacet ttttggatte agttagtata agetetteea
                                                                         180
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg
                                                                         240
                                                                         300
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc
ctttqtqcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc
                                                                         360
                                                                          402
aaqaqtcatc tgtctgcaaa agttgcgtta gtatatctgc ca
      <210> 192
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (601)
      <223> n = A, T, C or G
      <400> 192
gageteggat ceaataatet ttgtetgagg geageacaea tatneagtge eatggnaact ggtetaecee acatgggage ageatgeegt agntatataa ggteatteee tgagteagae
                                                                          60
                                                                          120
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt
                                                                         180
                                                                         240
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc
acqagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac
                                                                          300
                                                                         360
cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga
tacatetect gacagtactg aagaacttet tettttgttt caaaageare tettggtgee
                                                                          420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac
                                                                         480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag
                                                                         540
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca
                                                                          600
                                                                          601
      <210> 193
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (608)
      <223> n = A, T, C or G
      <400> 193
                                                                          60
atacagecea nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteact
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt
                                                                         120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg
                                                                         180
tkaagtgcag gaagaggctg accaectege ggtecaceag gatgccegae tgtgcgggae
                                                                         240
                                                                         300
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc
```

```
agaaccttcc qcctqttctc tqgcqtcacc tqcaqctqct qccqctqaca ctcqqcctcq
                                                                       360
gaccagcgga caaacggcrt tgaacagccg cacctcacgg atgcccagtg tgtcgcgctc
                                                                       420
caggammqsc accagcgtgt ccaggtcaat gtcggtgaag ccctccgcgg gtratggcgt
                                                                       480
ctgcaqtqtt tttgtcgatg ttctccaggc acaggctggc cagctgcggt tcatcgaaga
                                                                       540
gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggctcg cagttcttct tcaggaactc
                                                                       600
                                                                       608
cacgcaat
      <210> 194
      <211> 392
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(392)
      <223> n = A, T, C or G
      <400> 194
                                                                        60
quacggctgg accttgcctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt
ccagtecgag cageeccaga eegetgeege eegaagetaa geetgeetet ggeetteece
                                                                       120
                                                                       180
tccqcctcaa tqcaqaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac
                                                                       240
                                                                       300
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt
                                                                       360
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg
                                                                       392
aaataaatat agttattaaa ggttgtcant cc
      <210> 195
      <211> 502
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(502)
      <223> n = A, T, C or G
      <400> 195
                                                                        60
ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg
ccgagctgag gcagatgttc ccacagtgac ccccagagcc stgggstata gtytctgacc
                                                                       120
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc
                                                                       180
aagggaaggc cccattccgg ggstgttccc cgaggaggaa gggaaggggc tctgtgtgcc
                                                                       240
ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca
                                                                       300
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact
                                                                       360
                                                                       420
qsescacac cacceaqage acqccacceg ccatggggar tgtgctcaag gartegengg
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt
                                                                       480
                                                                       502
gctnanaaaa aaaaanaaaa aa
      <210> 196
      <211> 665
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (665)
      <223> n = A, T, C or G
      <400> 196
                                                                        60
qqttacttqq tttcattqcc accacttagt ggatqtcatt tagaaccatt ttgtctqctc
                                                                       120
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                       180
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkatc
                                                                       240
```

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aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt
                                                                        300 -
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact
                                                                        360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                        420
watatttatt tcattaattt ctttcctkqt ttacqtwaat tttqaaaaqa wtqcatgatt
                                                                        480
tettgacaga aategatett gatgetgtgg aagtagtttg acceacatee etatgagttt
                                                                        540
ttcttagaat gtataaaggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac
                                                                        600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan
                                                                        660
aagtg
                                                                        665
      <210> 197
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(492)
      <223> n = A, T, C or G
      <400> 197
ttttnttttt tttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat
                                                                         60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                        120
aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag
                                                                        180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
                                                                        240
caaaattcta ccctqaaact tactccatcc aaatattgga ataanagtca qcaqtgatac
                                                                        300
                                                                       360
attotottot gaacittaga ttttotagaa aaatatgtaa tagtgatoag gaagagotot
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                        420
                                                                        480
catttcactc ccatcacggg agtcaatgct acctgggaca cttgtatttt gttcatnctg
                                                                        492
anchtggctt aa
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (478)
      <223> n = A, T, C or G
      <400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa
                                                                        60
tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac
                                                                       120
tqaqtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
                                                                       180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat
                                                                       240
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag
                                                                        300
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta
                                                                       360
agcattetag tacetetact ccatggitaa gaategtaca ettatgttta catatginca
                                                                       420
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa
                                                                       478
      <210> 199
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (482)
      <223> n = A, T, C \text{ or } G
      <400> 199
                                                                        60
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta
```

```
tqctaqttcc tqtcatctat tcqctactaa atqcaqactq gaggggacca aaaaggggca
                                                                       120
tcaactccaq ciggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                       180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                       240
tgaaqccnac totgaacacq otggttatot nagatgagaa noagagaaat aaagtonaga
                                                                       300
aaatttacct ggangaaaag aggettingg etggggacca teccattgaa cettetetta
                                                                       360
anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg
                                                                       420
aacntngach neaccettnt ggaatanant ettgachgen teetgaactt geteetetge
                                                                       480
                                                                       482
      <210> 200
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (270)
      <223> n = A, T, C or G
      <400> 200
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc
                                                                        60
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                       120
aaggetgage tgacgeegea gaggtegtgt caegteecac gacettgaeg eegtegggga
                                                                       180
                                                                       240
cagccggaac agagcccggt gaangcggga ggcctcgggg agcccctcgg gaagggcggc
                                                                       270
ccgagagata cgcaggtgca ggtggccgcc
      <210> 201
      <211> 419
      <212> DNA
      <213> Homo sapien
      <221> misc_feature `
      <222> (1)...(419)
      <223> n = A, T, C or G
      <400> 201
                                                                        60
tttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg
                                                                       120
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
                                                                       180
                                                                       240
tggagtgggt gcaccetece tgtagaacet ggttacnaaa gettggggca gtteacetgg
tctgtgaccg tcattttctt gacatcaatg ttattagaag tcaggatatc ttttagagag tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga
                                                                       300
                                                                       360
aaaagttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                       419
      <210> 202
      <211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(509)
      <223> n = A, T, C or G
                                                                        60
tggcacttaa tccatttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
                                                                       120
ginattitino aaaatotaaa nnitattoaa atninagooa aantoottao noaaatnnaa
                                                                       180
tacnoncaaa aatcaaaaat atacntntot ttoagcaaac ttngttacat aaattaaaaa
                                                                       240
                                                                       300
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
ggaactaaaa taaaaaaaaa cactnccgca aaggttaaag ggaacaacaa attcntttta
                                                                       360
```

67

```
caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                           420
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca
                                                                           480
caatggnaat nccnccncnc tggactagt
                                                                           509
      <210> 203
      <211> 583
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (583)
      <223> n = A, T, C or G
      <400> 203
ttttttttt tttttttga ccccctctt ataaaaaaca agttaccatt ttatttact
                                                                            60
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac
                                                                           120
taaatqqaaa ctqccttaqa tacataattc ttaqqaatta qcttaaaatc tqcctaaaqt
                                                                           180
                                                                           240
gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc
attiticity totttaaaat tatctaatot ticcattitt tooctatice aagtoaatti getietetag ceteattee tagetettat etaetattag taagtggeti titteetaaa
                                                                           300
                                                                           360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
                                                                           420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                           480
tccattttag tcactaaacg atatcnaaag tgccagaatg caaaaggttt gtgaacattt
                                                                           540
attcaaaagc taatataaga tatttcacat actcatcttt ctg
                                                                           583
      <210> 204
      <211> 589
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
     · <222> (1) ··· (589)
      <223> n = A, T, C or G
      <400> 204
                                                                            60
ttttttttt tttttttt ttttttnctc ttctttttt ttganaatga ggatcgagtt
tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                           120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc
                                                                           180
                                                                           240
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt atttccatgc aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag
                                                                           300
                                                                           360
cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag
                                                                           420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc
                                                                           480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat
                                                                           540
ttattnagaa tgaattcaca tgttattatt contagooca acacaatgg
                                                                           589
      <210> 205
      <211> 545
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (545)
      <223> n = A, T, C or G
      <400> 205
tttttntttt tttttcagt aataatcaga acaatattta tttttatatt taaaattcat
                                                                            60
                                                                           120
agaaaaqtqc cttacattta ataaaaqttt qtttctcaaa qtqatcagag gaattagata
                                                                           180
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
```

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ttaaqatcat aqaqcttqta aqtqaaaaga taaaatttga cctcagaaac tctgagcatt
                                                                          240
aaaaatccac tattaqcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                          300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                          360
tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                          420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg
                                                                          480
aaggattaga tatgtttoot ttgccaatat taaaaaaata ataatgttta ctactagtga
                                                                          540
                                                                          545
aaccc
      <210> 206
      <211> 487
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (487)
      <223> n = A, T, C or G
ttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt
                                                                           60
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna
                                                                          120
caatttataa atqtaaqqtq ccattattga qtanatatat tcctccaaga gtggatgtgt
                                                                          180
cccttctccc accactaat gaancagcaa cattagttta attttattag tagatnatac
                                                                          240
actqctqcaa acqctaattc tcttctccat ccccatqtng atattqtqta tatqtqtag
                                                                          300
ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt
                                                                          360
tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cggtggcaag
                                                                          420
aactettega accepticet caaaggenge tgecacattt gtggentetn ttgcacttgt
                                                                          480
                                                                          487
ttcaaaa
      <210> 207
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(332)
      <223> n = A, T, C or G
      <400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa
                                                                           60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact
                                                                          120
gcatttatag gacettetgg tggttetget gttacntttg aantetgaca atcettgana atetttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagegca
                                                                          180
                                                                          240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg
                                                                          300
aaaaqaaqqc aqcctaggcc ctggggagcc ca
                                                                          332
      <210> 208
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(524)
      <223> n = A, T, C or G
      <400> 208
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
                                                                           60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat
                                                                          120
tttaaaqqac atqqaqcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac
                                                                         180
                                                                          240
teccqcqtqa ttcacattta gcaaccaaca atageteatg agtecatact tgtaaatact
```

```
tttgqcagaa tacttnttga aacttqcaga.tgataactaa gatccaagat atttcccaaa
                                                                        300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc
                                                                        360
atgageccag acactgacat caaactaage ccaettagae teetcaccae cagtetgtee
                                                                        420
tgicatcaga caggaggetg tcaccttgac caaattetca ccagtcaatc atctatccaa
                                                                        480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                        524
      <210> 209
      <211> 159
      <212> DNA
      <213> Homo sapien
      <400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg
                                                                         60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca
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tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat
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ccaggatgct aaatca
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                                                                        120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
                                                                       180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
                                                                       240
aaaaaaqqaq caaatgagaa gcct
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                                                                          180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta
                                                                          240
cccctacnac tctttactct ctgganaggg ccagtggtgg tagctataag cttggccaca
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ttttttttc ctttattcct ttgtcaga
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cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
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ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct
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tctcatcggt
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      <211> 444
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                                                                          120
tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac
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                                                                          240
ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat
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ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag
                                                                          360
agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt
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                                                                          444
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cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
                                                                          180
                                                                          240
ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct
tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa
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ggtgcc
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                                                                                    120
taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa atcaaaaatt tcctnaagtt ntcaagctat catatatact ntatcctgaa aaagcaacat
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                                                                                    260
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       <211> 262
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                                                                                    120
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ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt
                                                                                    180
                                                                                    240
atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta
atateettea tgettgtaaa gt
                                                                                    262
       <210> 218
       <211> 205
       <212> DNA
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       <220>
       <221> misc feature
       <222> (1)...(205)
<223> n = A,T,C or G
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                                                                                     60
                                                                                    120
                                                                                    180
                                                                                    205
anaaatcagc agacacaggt gtaaa
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       <211> 114
       <212> DNA
       <213> Homo sapien
       <400> 219
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accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga
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gagaaaatac tactttctcr aaatgtggcc gtccatcctc tttaractcm gcattgtgac	aaatggaagc ctttaragtt	ccttaaaggt gcatgacttg	gctttgatac gacacggtaa	tgaaggacac ctgttgcagt	240 300 320
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74

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togtggccga cotggcctct cotggcctgt ttottaagat goggagtcac atttcaatgg
                                                                       180
taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga
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tgctcggtgc acattggggt gctttgggat aaaagattta tgagccaact attctctggc
                                                                       300
accagattet aggecagttt gttecaetga agetttteee acageagtee acetetgeag
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gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt
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gagaaggeta ggatgettgt ctagtgttet tagetgteac gttggeteet tecaggttgg
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tigtatgiga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagtct
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caatataaag tootggttoa cactoaggaa ogagagotga occagttaag ggagaagttg
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cgggaaggga gagatgcctc cctctcattg aatgagcatc tccaggccct cctcactccg
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                                                                       301
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                                                                       180
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<210> 237 <211> 301

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                                                                            180
ccttggctaa tgcctcatag taggagtcct cagaccagcc atggggatca aacatatcct
ttgggtagtt ggtgccaagc tcgtcaatgg cacagaatgg atcagcttct cgtaaatcta
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qqqttccqaa attettett cettqqata atqtaqttca tatccattcc ctcctttatc
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                                                                            120
                                                                            180
cettgagact teeggagteg aggeteteea gggtteecea geceateaat cattttetge
accecetgee tgggaageag etceetgggg ggtgggaatg ggtgaetaga agggattea
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cataatacct tagaqatcaa gaaacattta cacaqttcaa ctgtttaaaa atagctcaac
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                                                                            120
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ctcctccatg tattggaaaa ctgcaaactg gactcaactg gaaggaagtg ctgctgccag
                                                                            180
tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtcttttct
                                                                            240
                                                                            300
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gtcttcaaga atatatcatt cctttttcac tagaacccat tcaaaatata agtcaagaat
                                                                          180
cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta
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tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcggcatga tgaccagcgt
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qctggtttgt ccaqatqqca agacaqtaqa aqcagaggct gcccacggga ctgtaacccg
                                                                          240
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                                                                          120
                                                                          180
aggtqttqta atgqtqaaaa cqtcttcctt ctttattqcc ccttcttatt tatqtqaaca
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aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat
                                                                          180
qttttcaaag agcagagatg caattaaata ttgtttagca tcaaaaaggc cactcaatac
                                                                          240
agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa
                                                                          300
                                                                          301
g
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      <211> 301
      <212> DNA
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acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata
                                                                         180
agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac
                                                                         240
taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc
caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa
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      <211> 301
      <212> DNA
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      <400> 247
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qcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttqttt cccccacqct
                                                                          120
gtgtcctgtg ttcaggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc
                                                                          180
ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc
                                                                          240
cttttcaaac catqaaqtca ggctctqtat ccctcctttt cctaactqat attctaacta
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                                                                          301
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acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag
                                                                          180
gtacattcca gcctqttggc aactccataa aaacatttca gattttaatc ccgaatttag
                                                                          240
ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc
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                                                                          301
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ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccgccc
                                                                          120
ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc
                                                                          180
categraatg aattatttg aaaattaatt ccaccatect tteagattet ggatggaaag
                                                                          240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt
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                                                                          120
cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac
                                                                          180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta
                                                                          240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc
                                                                          300
                                                                         301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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agacaacete atagageata ggagaactgg ttgccetggg ggcaggggga ctgtetggat ggcaggggtc etcaaaaatg ceactgteac tgccaggaaa tgettetgag cagtacacet
                                                                         120
                                                                         180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa
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cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct	300 301
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<210> 253 <211> 301 <212> DNA <213> Homo sapien	
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<210> 254 <211> 301 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 254 cgctgcgcct ttcccttggg ggaggggcaa ggccagaggg ggtccaagtg cagcacgagg aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaaatcccc ccaaatctct tcatcttacc ctggtggact cctgactgta gaatttttg gttgaaacaa gaaaaaaata aagctttgga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc t</pre>	60 120 180 240 300 301
<210> 255 <211> 302 <212> DNA <213> Homo sapien	
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<210> 256 <211> 301 <212> DNA <213> Homo sapien	
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aggaccetce tecceacace teaatecace aaaccateca taatgeacee agataggeee
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acceccaaaa geetggacae ettgageaca cagttatgae caggacagae teatetetat
                                                                            180
aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt
                                                                            240
gtggcctctc ggcctggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt
                                                                            300
                                                                            301
      <210> 257
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 257
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tocccactta tttttgtott toactatogo aggoottaga agaggtotac otgootocag
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tottacctag tocagtotac cocctggagt tagaatggcc atcctgaagt gaaaagtaat
                                                                            180
gtcacattac tcccttcagt gatttcttgt agaagtgcca atccctgaat gccaccaaga
                                                                            240
tettaatett cacatettta atettatete titgaeteet etttacaceg gagaaggete
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                                                                            301
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      <211> 301
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      <220>
      <221> misc_feature
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\langle 223 \rangle n = A,T,C or G
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aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg
                                                                            120
                                                                            180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat
                                                                            240
tgqtgatccc tgggaqcgcc ggtgqaqtaa cgttqqtcca tggaaagcag cgcccacaac
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                                                                            301
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      <211> 301
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gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa
                                                                            120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt
                                                                            180
                                                                            240
tocageteae ateteatetg catgeageae ggaceggatg egeceaetgg gtettggett
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coctcocate tteteaagea gtgteettgt tgagecattt geateettgg etecaggtgg
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<211> 301

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<212> DNA
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                                                                       120
agaactqtaa caqccacaqt tqqccatttc atqccaatqq caqcaaacaa caqqattaac
                                                                       180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc
                                                                       240
actgagacat cagtacctgc cogggeggcc gctcgagccg aattctgcag atatccatca
                                                                       300
                                                                       301
      <210> 261
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 261
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tetgetteca tecaegatte tageaatgae eteteggaea teaaagetee tettaaggtt
                                                                       120
                                                                       180
agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aaggttcaat
ggtgacatcc aatttettet gataatttag atteetcaca acetteetag ttaagtgaag
                                                                       240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctgc aatgaagatc
                                                                       300
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 262
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tgtgagette ttgccgcaag tetetcagaa atttaaaaag atgcaaatee etgagteace
                                                                       120
cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga
                                                                       180
gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgccc
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      <211> 301
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                                                                       120
ttcttagtat tatttatggt aaataggctc ttaccacttg caaataactg gccacatcat
                                                                       180
                                                                       240
taatgactga cttcccagta aggeteteta aggggtaagt angaggatee acaggatttg
                                                                       300
agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg
                                                                       301
      <210> 264
      <211> 301
      <212> DNA
      <213> Homo sapien
                                                                        60
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82

aatgaatgac tctaaaaaca atatttacat ttaatggttt gtagacaata aaaaaacaag 120 qtqqatagat ctagaattgt aacattttaa gaaaaccata scatttgaca qatqagaaag 180 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240 accettcata taaattcact atettggett gaggeactee ataaaatgta teaegtgeat 300 301 <210> 265 <211> 301 <212> DNA <213> Homo sapien <400> 265 tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcatctttgt 60 cttcttgtga cgcagtattt cttctctggg gagaagccgg gaagtcttct cctggctcta 120 catattettg gaagteteta ateaactitt gtteeattig ttteatttet teaggaggga 180 ttttcaqttt qtcaacatqt tctctaacaa cacttqccca tttctqtaaa qaatccaaaq 240 cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg 300 301 <210> 266 <211> 301 <212> DNA <213> Homo sapien <400> 266 taccgtctgc ccttcctccc atccaggcca tctgcgaatc tacatgggtc ctcctattcg 60 acaccagate actettteet etaccacag gettgetatg ageaagagae acaaceteet 120 ctcttctqtq ttccaqcttc ttttcctqtt cttcccaccc cttaaqttct attcctqqqq 180 240 atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca gggtgcacag 300 cacagactee tgacaactgg taaggecaat gaactgggag eteacagetg\_getgtgeetg 301 <210> 267 <211> 301 <212> DNA <213> Homo sapien <400> 267 aaagagcaca ggccagctca gcctgcctg gccatctaga ctcagcctgg ctccatgggg 60 120 gttctcagtg ctgagtccat ccaggaaaag ctcacctaga ccttctgagg ctgaatcttc atcctcacag gcagcttctg agagcctgat attcctagcc ttgatggtct ggagtaaagc 180 ctcattctga ttcctctcct tcttttcttt caagttggct ttcctcacat ccctctgttc 240 aattogotto agottgtotg otttagooot catttocaga agottottot otttggoato 300 301 <210> 268 <211> 301 <212> DNA <213> Homo sapien <400> 268 aatgtctcac tcaactactt cccagcctac cgtggcctaa ttctgggagt tttcttctta 60 gatcttggga gagctggttc ttctaaggag aaggaggaag gacagatgta actttggatc 120 tcgaagagga agtctaatgg aagtaattag tcaacggtcc ttgtttagac tcttggaata 180 tgctgggtgg ctcagtgagc ccttttggag aaagcaagta ttattcttaa ggagtaacca 240 cttcccattq ttctactttc taccatcatc aattqtatat tatqtattct ttqqaqaact 300 301 <210> 269 <211> 301 <212> DNA

<213> Homo sapien

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aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact
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atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta
                                                                       180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta
                                                                       240
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc
                                                                       300
                                                                       301
      <210> 270
      <211> 301
      <212> DNA
      <213> Homo sapien
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cacaagaata catatteett ttatttetaa ggagttaaac atagatgtag etgatgtgga
                                                                       120
gagettgetg gtgcagtgca tattggataa cactatteat ggccgaattg atcaagtcaa
                                                                       180
ccaactcctt gaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa
                                                                       240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac
                                                                       300
                                                                       301
      <210> 271
      <211> 301
      <212> DNA
      <213> Homo sapien
      <221> misc_feature
      <222> (1) ... (301)
     \cdot<223> n = A,T,C or G
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tttatagete atetttaggg ttgatattea gtteatgett eeettgetgt tettgateea
                                                                       120
                                                                       180
gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaagg
tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt
                                                                       240
teteteetee agatganaac tqateatqeq eccacatttt qqqttttata qaaqeaqtea
                                                                       300
                                                                       301
      <210> 272
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 272
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                                                                        60
ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga
                                                                       120
tccaataatt ccctcatgat gagcaagaaa aattctttgc gcacccctcc tgcatccaca
                                                                       180
gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc
                                                                       240
ctaaggactt ccattgcatc tcctacaata ttttctctac gcaccactag aattaagcag
                                                                       300
                                                                       301
      <210> 273
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
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quaccettta aaaataaaat ttaccatett dtatatteet tataetatee ttatteace
                                                                        180
ttytttctgt ccaqaqaqaq tatcaqtqac ananatttma qqqtqaamac atgmattqqt
                                                                        240
gggacttnty tttacngagm accetgeecg sgegeecteg makengantt eegesanane
                                                                        300
                                                                       301
      <210> 274
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 274
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                                                                       120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttgtg gaaaagtcca
                                                                       180
totaggtatg gitgcattot cgtottottt totgcagtag ataatgaggt aaccgaaggo
                                                                       240
                                                                       300
aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc
С
                                                                       301
      <210> 275
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C \text{ or } G
      <400> 275
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qqqtqaaatt qqccaacttt ctattaactt atqttqqcaa ttttqccacc aacaqtaaqc
                                                                       120
                                                                       180
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag
tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc
                                                                       240
agatatecat cacaetggeg gnegetegan catgeateta gaaggneeaa ttegeeetat
                                                                       300
                                                                       301
а
      <210> 276
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 276
tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat
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ttatcatgtg acttctaatt agaaatgta tccaaaagca aaacagcaga tatacaaaat
                                                                       120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc
                                                                       180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt
                                                                       240
aaaactattc agtatgtttc cettgettca tgtctgagaa ggeteteett caatggggat
                                                                       300
                                                                       301
      <210> 277
      <211> 301
      <212> DNA
      <213> Homo sapien
```

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<220>
       <221> misc_feature
       <222> (1)...(301)
       <223> n = A, T, C or G
       <400> 277
 tttgttgatg tcagtatttt attacttgcg ttatgagtgc tcacctggga aattctaaag
                                                                            60
 atacaqaqqa cttqqaqqaa gcaqaqcaac tgaatttaat ttaaaaqaag gaaaacattg
                                                                           120
 quatcatqqc actoctqata otttoccaaa toaacactot caatqcccca coctoqtoot
                                                                           180
 caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga
                                                                           240
 gttenetgte gattacatet gaccagtete ettttteega agteenteeg tteaatettg
                                                                           300
                                                                           301
       <210> 278
       <211> 301
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(301)
       <223> n = A, T, C or G
       <400> 278
                                                                            60
 taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat
 aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca
                                                                           120
 cagtetetae tgttattatg cattacetgg gaatttatat aageeettaa taataatgee
                                                                           180
 aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgct tcacaggttt
                                                                           240
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt
                                                                           300
                                                                           301
       <210> 279
       <211> 301
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(301)
       <223> n = A, T, C or G
       <400> 279
 aaagcaggaa tgacaaagct tgcttttctq gtatqttcta ggtgtattgt gacttttact
                                                                            60
 gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc
                                                                           120
 ttagacettt acettecage caceccacag tgettgatat tteagagtea gteattggtt
                                                                           180
 atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag
                                                                           240
                                                                           300
                                                                           301
       <210> 280
       <211> 301
       <212> DNA
     <213> Homo sapien
       <400> 280
 ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg
                                                                            60
 tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct
                                                                           120
                                                                           180
 tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
 gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga
                                                                           240
 cagactatta actocacagt taattaagga qqtatqttoc atqtttattt gttaaagcag
                                                                           300
                                                                           301
```

```
<210> 281
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 281
aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc
                                                                           60
gccgagcaat ccaaatcctg aatgaagggg catcttctga aaaaggagat ctgaatctca atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa
                                                                          120
                                                                          180
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc
                                                                          240
tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc
                                                                          300
                                                                          301
      <210> 282
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 282
caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca
                                                                           60
tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga
                                                                          120
agegeagaag caaageecag geagaaceat getaacetta cageteagee tgeacagaag
                                                                          180
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg
                                                                          240
cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag
                                                                          300
                                                                          301
      <210> 283
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 283
atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag
                                                                           60
cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca
                                                                          120
gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc
                                                                          180
acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcatctttta
                                                                          240
ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttgcttt
                                                                          300
                                                                          301
      <210> 284
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 284
caggtacaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt
                                                                           60
qcttcqtqtq tqqqcaaaqc aacatcttcc ctaaatatat attaccaaqa aaaqcaaqaa
                                                                          120
                                                                          180
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt
                                                                          240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt
                                                                          300
                                                                          301
      <210> 285
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
```

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<400> 285
acatcaccat gatcggatcc cccacccatt atacgttgta tgtttacata aatactcttc
                                                                         60
aatgatcatt agtgttttaa aaaaaatact gaaaactcct tctgcatccc aatctctaac
                                                                        120
caggaaagca aatgctattt acagacctgc aagccctccc tcaaacnaaa ctatttctgg
                                                                        180
attaaatatg tetgaettet tttgaggtea caegaetagg caaatgetat ttaegatetg
                                                                        240
caaaagctgt ttgaagagtc aaagccccca tgtgaacacg atttctggac cctgtaacag
                                                                        300
                                                                        301
      <210> 286
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 286
taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaa aaactttgct
                                                                         60
tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagatttttt
                                                                        120
atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca
                                                                        180
aaaataagct accatatagc ttataagtct caaatttttg ccttttacta aaatgtgatt
                                                                        240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg
                                                                        300
                                                                        301
      <210> 287
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 287
                                                                         60
tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg
                                                                        120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accetetgce
                                                                        180
ccgtggttat ctcctcccca gcttggctgc ctcatgttat cacagtattc cattttgttt
                                                                        240
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc
                                                                        300
                                                                        301
      <210> 288
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 288
qtacacctaa ctqcaaqqac aqctqaqqaa tqtaatqqqc aqccqctttt aaaqaaqtaq
                                                                         60
agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa
                                                                        120
gatetttaaa gacaatttea agagaatatt teettaaagt tggcaatttg gagateatae
                                                                        180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
                                                                        240
tctgccttaa ttttggatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa
                                                                        300
                                                                        301
      <210> 289
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C \text{ or } G
      <400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgctcc tggaaactta
                                                                        60
acttttgatg tetecaagta gtecacette atttaactet ttgaaactgt atcatetttg
                                                                       120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa
                                                                       180
```

```
cqttctataa atqaatqtqc tgaaqcaaaq tqcccatqqt qqcqqcqaan aaqaqaaaqa
                                                                       240
tgtgttttgt tttggactct ctgtggtccc ttccaatgct gtgggtttcc aaccagngga
                                                                       300
                                                                        301
      <210> 290
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
      <400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac
                                                                         60
tgactgatct gttcatitct ctcacagetc ttacccccaa aagettttcc accctaagtg
                                                                       120
                                                                       180
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatg
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc
                                                                       240
                                                                       300
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag
                                                                       301
      <210> 291
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttgttgaa acataacaac
                                                                         60
tatatcagct agatttttt tctatqcttt acctqctatq qaaaatttqa cacattctqc
                                                                       120
                                                                       180
tttactcttt tgtttatagg tgaatcacaa aatgtatttt tatgtattct gtagttcaat
                                                                       240
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa
acatgagett cactteecca ctaactaatt ageatetgtt atttettaac egtaatgeet
                                                                       300
                                                                       301
      <210> 292
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
      <400> 292
                                                                        60
accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc
tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggtattc
                                                                       120
aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg
                                                                       180
ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc
                                                                       240
tcactacaca cacagacccc acagtectat atgccacaaa cacattteca taacttgaaa
                                                                       300
                                                                       301
      <210> 293
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 293
ggtaccaagt gctggtgcca gcctgttacc tgttctcact gaaaagtctg gctaatgctc
                                                                        60
ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt
                                                                       120
aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt
                                                                       180
```

```
qtqaqaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tqtacctcgg
                                                                     240
ccqcqaccac gctaagccqa attctqcaga tatccatcac actqgcggcc gctcgagcat
                                                                     300
                                                                     301
      <210> 294
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
      <400> 294
tgacccataa caatatacac tagctatctt tttaactgtc catcattagc accaatgaag
                                                                      60
attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag
                                                                     120
tttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tgaaaataag
                                                                     180
ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc
                                                                     240
                                                                     300
cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt
                                                                     301
      <210> 295
      <211> 305
      <212> DNA
      <213> Homo sapien
gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta
                                                                     60
120
                                                                     180
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatggt.
                                                                     240
totcagaacc atttcaccca gacagoctgt ttctatcctg tttaataaat tagtttgggt
                                                                     300
                                                                     305
tctct
      <210> 296
      <211> 301
      <212> DNA ·
      <213> Homo sapien
                                                                     60
aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg
                                                                    120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac
                                                                     180
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt
                                                                    240
tqtcattact ataaatttta aaatctqtta ataaqatqqc ctataqqqaq qaaaaaqqqq
                                                                     300
                                                                     301
      <210> 297
      <211> 300
      <212> DNA *
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1) ... (300)
     <223> n = A, T, C or G
     <400> 297
actgagtttt aactggacge caagcaggca aggetggaag gttttgetet etttgtgeta
                                                                     60
aaggttttga aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga
                                                                    120
                                                                    180
acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt
```

```
tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc
                                                                                                                                                                        240
acceptance acceptance acceptance quantity and acceptance acceptanc
                                                                                                                                                                        300
               <210> 298
               <211> 301
               <212> DNA
               <213> Homo sapien
               <220>
               <221> misc_feature
               <222> (1) ... (301)
               <223> n = A, T, C or G
               <400> 298
60
                                                                                                                                                                        120
                                                                                                                                                                        180
                                                                                                                                                                        240
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg
                                                                                                                                                                        300
                                                                                                                                                                        301
               <210> 299
               <211> 301
               <212> DNA
               <213> Homo sapien
               <400> 299
gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggtctctgc
                                                                                                                                                                          60
teactgeace etetgeetee caggitegag caatteteet geeteageet eecaggtage
                                                                                                                                                                        120
                                                                                                                                                                        180
tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg
                                                                                                                                                                        240
qaqtttcqcc atgttggcca gctggtctca aactcctgac ctcaagcgac ctgcctgcct
cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt
                                                                                                                                                                        300
                                                                                                                                                                        301
              <210> 300
               <211> 301
              <212> DNA
               <213> Homo sapien
              <400> 300
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                                                                                                                                                                          60
tatgtcccac acccactggg aaaggctccc acctggctac ttcctctatc agctgggtca
                                                                                                                                                                        120
gctgcattcc acaaggttct cagcctaatg agtttcacta cctgccagtc tcaaaactta
                                                                                                                                                                        180
gtaaagcaag accatgacat teeeccaegg aaatcagagt ttgeeccaee gtettgttae tataaageet geetetaaca gteettgett etteacaeca ateeegageg cateeeccat
                                                                                                                                                                        240
                                                                                                                                                                        300
                                                                                                                                                                        301
              <210> 301
              <211> 301
              <212> DNA
              <213> Homo sapien
              <400> 301
ttaaattttt gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagtctgc
                                                                                                                                                                          60
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt gggaactcac aaagaccctc agagctgaga cacccacaac agtgggagct cacaaaagacc
                                                                                                                                                                        120
                                                                                                                                                                       180
ctcagagctg agacacccac aacagtggga gctcacaaag accctcagag ctgagacacc
                                                                                                                                                                        240
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt
                                                                                                                                                                        300
                                                                                                                                                                        301
t
              <210> 302
```

<210> 302 <211> 301

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<212> DNA
      <213> Homo sapien
      <400> 302
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                                                                        60
tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac
                                                                       120
                                                                       180
tigagtiggt tottagtatt attitatggta aataggetet taccactige aaataactgg
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
                                                                       240
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccctctta ttttcagagg
                                                                       300
                                                                       301
      <210> 303
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 303
aggtaccaac tgtggaaata ggtagaggat cattttttct ttccatatca actaagttgt
                                                                        60
atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac
                                                                       120
tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc
                                                                       180
agtaacqqqt atqtttttct aactqatctt ttqctcqttc caaaqqqacc tcaaqacttc
                                                                       240
categatitt atatetgggg tetagaaaag gagttaatet gtttteecte ataaatteae
                                                                       300
                                                                       301
      <210> 304
     <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 304
acatggatgt tattttgcag actgtcaacc tgaatttgta tttgcttgac attgcctaat
                                                                        60
tattagtttc agtttcagct tacccacttt ttgtctgcaa catgcaraas agacagtgcc
                                                                       120
ctttttagtg tatcatatca ggaatcatct cacattggtt tgtgccatta ctggtgcagt
                                                                       180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga
                                                                       240
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct
                                                                       300
                                                                       301
      <210> 305
    <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (301)
      <223> n = A, T, C or G
                                                                        60
gangtacage gtggtcaagg taacaagaag aaaaaaatgt gagtggcate etgggatgag
cagggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggcg
                                                                       120
                                                                       180
taaaqqaqqa qaaacaqata caaaatctcc aactcaqtat taaqqtattc tcatgcctag
                                                                       240
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa
ttctgqqatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag
                                                                       300
                                                                       301
      <210> 306
      <211> 8
      <212> PRT
      <213> Homo sapien
      <400> 306
Val Leu Gly Trp Val Ala Glu Leu
```

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1
       <210> 307
       <211> 637
       <212> DNA
       <213> Homo sapien
       <400> 307
acagggratg aagggaaagg gagaggatga ggaagccccc ctgggggattt ggtttggtcc
                                                                             60
ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatccagaa ataggggcac
                                                                            120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt
                                                                           180
cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca
                                                                            240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga
                                                                            300
gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgtg
                                                                            360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga
                                                                            420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa
                                                                            480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca
                                                                           540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg
                                                                            600
ttacagatac tggggcagca aataaaactg aatcttg
                                                                           637
      <210> 308
      <211> 647
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (647)
      <223> n = A, T, C or G
      <400> 308
                                                                            60
acqattttca ttatcatgta aatcgggtca ctcaaggggc caaccacagc tgggagccac
tgctcagggg aaggttcata tgggactttc tactgcccaa ggttctatac aggatataaa
                                                                           120
qqnqcctcac aqtataqatc tqqtaqcaaa qaaqaaqaaa caaacactqa tctctttctq
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ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg
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                                                                           360
                                                                           420
gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac
                                                                           480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca
                                                                           540
                                                                           600
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aatgtccttt tttttctcct gcttctgact tgataaaagg ggaccgt
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gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtccg
                                                                           180
                                                                           240
ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag
                                                                           300
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc
                                                                           360
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat
                                                                           420
                                                                           460
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                                                                       120
taggaaaqag aaacacaqaa ggaagaqaca caataaaagt cattatgtat tctgtgagaa
                                                                       180
gtcagacagt aagatttgtg ggaaatgggt tggtttgttg tatggtatgt attttagcaa
                                                                       240
taatctttat ggcagagaaa gctaaaatcc tttagcttgc gtgaatgatc acttgctgaa
                                                                       300
ttcctcaagg taggcatgat gaaggagggt ttagaggaga cacagacaca atgaactgac
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ctagatagaa agccttagta tactcagcta ggaatagtga ttctgagggc acactgtgac
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atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc
                                                                       480
atattttcac ccccacaaa qtcaqttaaa tattqqqaca ctaaccatcc aqqtcaaqa
                                                                       539
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      <211> 526
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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                                                                       120
catttacagc atttaaaatg tgttcagcat gaaatattag ctacagggga agctaaataa
                                                                       180
attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg
                                                                       240
tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa
                                                                       300
aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc
                                                                       360
tetetttaca gggageteet geagececta eagaaatgag tggetgagat tettgattge
                                                                       420
acagcaagag cttctcatct aaaccctttc cctttttagt atctgtgtat caagtataaa
                                                                       480
agttctataa actgtagtnt acttatttta atccccaaag cacagt
                                                                       526
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      <211> 500
      <212> DNA
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ccatttetet tteeetteea eetgeeagtt ttgetgaete teaacttgte atgagtgtaa
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gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg
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gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atcccctctt
                                                                       300
tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct
                                                                       360
tgctaatgtg gtitcctttg taaaccanga ttcttatttg nctggtatag aatatcagct
                                                                       420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt
                                                                       480
                                                                       500
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      <221> misc feature
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                                                                        120
                                                                        180
 ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa
 gtagtgacat gtttttgcac atttccagcc cttttaaata tccacacaca caggaaqcac
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 aaaaggaagc acagagatcc ctgggagaaa tgcccggccg ccatcttggg tcatcgatga
                                                                        300
                                                                        360
 gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg
 ttccttaaag gatggcagga aaacagatcc tgttgtggat atttatttga acgggattac
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 aqatttqaaa tqaaqtcaca aagtgagcat taccaatgag aggaaaacag acgagaaaat
                                                                        480
 cttgatggtt cacaagacat gcaacaaaca aaatggaata ctgtgatgac acgagcagcc
                                                                        540
 aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg
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 cgttatacca atcatttcta tttctaccct caaacaagct gtngaatatc tgacttacgg
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 ticttntqqc ccacattttc atnatccacc contentttt aannttantc caaantgt
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       <211> 358
       <212> DNA
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 caacatqtqt aqatctcttq tcttattctt ttqtctataa tactqtattq tqtaqtccaa
                                                                        180
                                                                        240
 gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc
ttgttgtatt getgaactgt agtgeeetgt attttgette tgtetgtgaa ttetgttget
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                                                                        120
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 gacccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag ccccaatgac
                                                                        180
                                                                        240
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 tagettetge tgtaagaggg tgttgteeeg ggggetegtg eggttattgg teetgggett
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                                                                         60
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gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg
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tgggggcggt ttatcaggca gtgataaaca t
                                                                       151
     <210> 319
     <211> 151
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    · <213> Homo sapien
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catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg
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taagattggg tttatgtgat tttagtgggt a .
                                                                       151
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      <211> 150
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gagcggctgc ccttttttt ttttttttt ggggggaatt ttttttttt aatagttatt
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     <211> 151
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tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg
                                                                       120
tgcctctgag aaatcaaagt cttcatacac t
                                                                       151
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attgtgcagg gctcgcttca nacttccagt t
                                                                       151
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     <211> 151
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     <221> misc_feature
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<222> (1)...(151)
      <223> n = A, T, C or G
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nagactcant tactacccag tttgtggttt twtgggagaa atgtaactgg acagttagct
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                                                                         151
gttcaatyaa aaagacactt ancccatgtg g
      <210> 324
      <211> 461
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (461)
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gcgaacctca cttctagact ttcacggtgg gacgaaacgg gttcagaaac tgccaggggc
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ctcatacagg gatatcaaaa taccetttgt getacceagg ccctggggaa teaggtgact
cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
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gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
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aaaaacgcac aagagcccct gccctgccct agctgangca c
                                                                         461
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                                                                         180
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20 25 30 Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly	
35 40 45 Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu	
50 55 60 Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala	
65 70 75 80 Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp	
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100 105 110 Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro	
115 120 125 Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys	
130 135 140 Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly	
145 150 . 155 160 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro	
165 170 175	
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala 180 185 190	
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Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
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His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
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			aacaaaaacc			1920
			aacaaaaaaa			1980
			ggtcaattta			2040
			tgtgccaaaa			2100
			agtctaagga			2160
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PCT/US00/27464 WO 01/25272

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Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr

His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp
115 120 125

105

110

Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp 135 140 Val Asn Lys Arg Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser 150 155 Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys 170 165 175 Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala 180 185 190 Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly 195 200 205 Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr 215 220 Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Tyr 225 230 235 240 235 230 Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu 245 250 255 Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys 260 265 Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu 275 280 285 275 280 285 Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu 290 295 300 Glu Gln Asn Val Asp Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu 310 Ser Met Leu Phe Leu Val Ile Ile Met 325 <210> 377 <211> 148

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<213> Homo sapien

<220>

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Lys Asn Lys Val

145

<210> 378

<211> 1719

<212> PRT

117

## <213> Homo sapien

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180 185 190 185 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr 200 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met 210 215 220 215 220 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn 230 235 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys 245 250 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly 260 265 270 Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val 280 285 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr 295 300 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile 310 315 Val Ser Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu 325 330 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val 340 345 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile 355 360 365 Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys 375 380 Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser 385 390 395 400 390 395 Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys 405 410 415Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly 425 Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys 440 435 445 Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly 455 460 Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys

465					470					475					480
Thr	Leu	Arg	Asn	Lys 485	Met	Gly	Lys	Trp	Cys 490	Cys	His	Cys	Phe	Pro 495	Cys
Cys	Arg	Gly	Ser 500	Gly	Lys	Ser	Lys	Val 505	Gly	Ala	Trp	Gly	Asp 510	Tyr	Asp
Asp	Ser	Ala 515	Phe	Met	Glu	Pro	Arg 520	Tyr	His	Val	Arg	Gly 525	Glu	Asp	Leu
Asp	Lys 530	Leu	His	Arg	Ala	Ala 535	Trp	Trp	Gly	Lys	Val 540	Pro	Arg	Lys	Asp
Leu 545	Ile	Val	Met	Leu	Arg 550	Asp	Thr	Asp	Val	Asn 555	Lys	Lys	Asp	Lys	Gln 560
•				565					570	Asn	-			575	
	_		580		_	_	_	585		Leu			590	_	
_	_	595					600			Gln		605			
_	610					615				Asp	620				_
625	-	_			630			_		11e 635	_			_	640
			_	645				_	650	Ala	_			655	_
	_		660					665		Gly			670		
		675					680			Lys	•	685			
	690	•	•	•		695				Leu	700		-	-	-
705					710					Gln 715			-		720
		_		725	_				730	Glu	_			735	
			740		_			745		Asp	_	-	750	-	
		755					760			Pro		765			
	770					775		_		Lys	780				
785			-		790					795		-	_	_	800
-				805			-	-	810	Glu				815	-
			820					825		Ala Pro			830	_	
_		835			-	-	840	_		Ile		845			
	850					855				Ser	860				
865					870					875					880
				885					890	Glu				895	
	_		900		_			905		Glu			910		
		915					920			Val		925			
	930					935				Asp	940				
945	_			_	950					Gln 955					960
Asn	GIU	GIU	ryr	пıs	ser	Asp	GIU	GTU	ASN	Asp	rnr	GTU	гÀ2	GID	rue

	965	970		975
Cys Glu Glu Gln 980			Asp Glu Ile	
Glu Glu Lys Gln 995	Ile Glu Val		Met Asn Ser 100	Glu Leu Ser
Leu Ser Cys Lys 1010	Lys Glu Lys 101		His Glu Asn 1020	Ser Thr Leu
Arg Glu Glu Ile 1025	Ala Met Leu 1030	Arg Leu Glu	Leu Asp Thr 1035	Met Lys His 104
Gln Ser Gln Leu	Pro Arg Thr 1045	His Met Val		Asp Ser Met 1055
Pro Ala Ala Ser 106		Lys Pro Phe 1065	Gly Leu Arg	Ser Lys Met 1070
Gly Lys Trp Cys 1075	Cys Arg Cys	Phe Pro Cys 1080	Cys Arg Glu 108	
Ser Asn Val Gly 1090	Thr Ser Gly		Asp Ser Ala 1100	Met Lys Thr
Leu Arg Ser Lys 1105	Met Gly Lys 1110	Trp Cys Arg	His Cys Phe 1115	Pro Cys Cys 112
Arg Gly Ser Gly	Lys Ser Asn 1125	Val Gly Ala 1130		His Asp Asp 1135
Ser Ala Met Lys 114		Asn Lys Met 1145	Gly Lys Trp	Cys Cys His 1150
Cys Phe Pro Cys 1155	Cys Arg Gly	Ser Gly Lys 1160	Ser Lys Val	
Gly Asp Tyr Asp 1170	Asp Ser Ala		Pro Arg Tyr 1180	His Val Arg
Gly Glu Asp Leu 1185	Asp Lys Leu 1190	His Arg Ala	Ala Trp Trp	Gly Lys Val
Pro Arg Lys Asp	Leu Ile Val 1205	Met Leu Arg 1210		Val Asn Lys 1215
Lys Asp Lys Gln		Ala Leu His	Leu Ala Ser	Ala Asn Gly
122	U	1225		1230
Asn Ser Glu Val 1235		· -	Arg Arg Cys	Gln Leu Asn
Asn Ser Glu Val	Val Lys Leu	Leu Leu Asp 1240 Thr Ala Leu	124	Gln Leu Asn 5
Asn Ser Glu Val 1235 Val Leu Asp Asn	Val Lys Leu Lys Lys Arg 125	Leu Leu Asp 1240 Thr Ala Leu 5	124 Ile Lys Ala 1260	Gln Leu Asn 5 Val Gln Cys
Asn Ser Glu Val 1235 Val Leu Asp Asn 1250 Gln Glu Asp Glu	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu	124 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr	Gln Leu Asn 5 Val Gln Cys Thr Asp Pro 128
Asn Ser Glu Val 1235 Val Leu Asp Asn 1250 Gln Glu Asp Glu 1265	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290	124 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr	Gln Leu Asn 5 Val Gln Cys Thr Asp Pro 128 Ala Ile Tyr 1295
Asn Ser Glu Val	Val Lys Leu Lys Lys Arg 125. Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr Leu Leu Tyr Pro Leu Leu 132	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val
Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys	Val Lys Leu Lys Lys Arg 125. Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr Leu Leu Tyr Pro Leu Leu 132	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val
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Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys 1315  His Glu Gln Lys 1330  Asn Leu Asn Ala	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His Gln Gln Val 133 Leu Asp Arg 1350	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe 5 Tyr Gly Arg	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr 0 Leu Leu Tyr Pro Leu Leu 132 Leu Ile Lys 1340 Thr Ala Leu 1355 Leu Leu Leu Leu	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val  Lys Lys Ala  Ile Leu Ala 136
Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys 1315  His Glu Gln Lys 1330  Asn Leu Asn Ala 1345	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala O Asn Lys His Gln Gln Val 133 Leu Asp Arg 1350 Ser Ala Ser 1365 Ser Gln Asp	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe 5 Tyr Gly Arg Ile Val Ser	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr 0 Leu Leu Tyr Pro Leu Leu 132 Leu Ile Lys 1340 Thr Ala Leu 1355 Leu Leu Leu	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val  Lys Lys Ala  Ile Leu Ala 136  Glu Gln Asn 1375
Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys 1315  His Glu Gln Lys 1330  Asn Leu Asn Ala 1345  Val Cys Cys Gly  Ile Asp Val Ser	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His Gln Gln Val 133 Leu Asp Arg 1350 Ser Ala Ser 1365 Ser Gln Asp	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe 5 Tyr Gly Arg Ile Val Ser 1370 Leu Ser Gly 1385	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr  Leu Leu Tyr  Pro Leu Leu 132 Leu Ile Lys 1340 Thr Ala Leu 1355 Leu Leu Leu Leu 0 Gln Thr Ala	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val  Lys Lys Ala  Ile Leu Ala 136  Glu Gln Asn 1375  Arg Glu Tyr 1390  Ser Asp Tyr
Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys 1315  His Glu Gln Lys 1330  Asn Leu Asn Ala 1345  Val Cys Cys Gly  Ile Asp Val Ser 138  Ala Val Ser Ser	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His Gln Gln Val 133 Leu Asp Arg 1350 Ser Ala Ser 1365 Ser Gln Asp 0 His His His	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe 5 Tyr Gly Arg Ile Val Ser 1370 Leu Ser Gly 1385 Val Ile Cys 1400 Ile Ser Ser	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr  Leu Leu Tyr  Pro Leu Leu 132 Leu Ile Lys 1340 Thr Ala Leu 1355 Leu Leu Leu Gln Thr Ala Gln Leu Leu 140	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val  Lys Lys Ala  Ile Leu Ala 136  Glu Gln Asn 1375  Arg Glu Tyr 1390  Ser Asp Tyr 5
Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys 1315  His Glu Gln Lys 1330  Asn Leu Asn Ala 1345  Val Cys Cys Gly  Ile Asp Val Ser 138  Ala Val Ser Ser 1395  Lys Glu Lys Gln	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His Gln Gln Val 133 Leu Asp Arg 1350 Ser Ala Ser 1365 Ser Gln Asp 0 His His His Met Leu Lys 141	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe 5 Tyr Gly Arg Ile Val Ser 1370 Leu Ser Gly 1385 Val Ile Cys 1400 Ile Ser Ser 5	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr  Leu Leu Tyr  Pro Leu Leu 132 Leu Ile Lys 1340 Thr Ala Leu 1355 Leu Leu Leu 0 Gln Thr Ala Gln Leu Leu 140 Glu Asn Ser 1420	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val  5  Lys Lys Ala  Ile Leu Ala 136  Glu Gln Asn 1375  Arg Glu Tyr 1390  Ser Asp Tyr  5  Asn Pro Glu
Asn Ser Glu Val 1235  Val Leu Asp Asn 1250  Gln Glu Asp Glu 1265  Asn Ile Pro Asp  Asn Glu Asp Lys 130  Ile Glu Ser Lys 1315  His Glu Gln Lys 1330  Asn Leu Asn Ala 1345  Val Cys Cys Gly  Ile Asp Val Ser 138  Ala Val Ser Ser 1395  Lys Glu Lys Gln 1410  Gln Asp Leu Lys	Val Lys Leu Lys Lys Arg 125 Cys Ala Leu 1270 Glu Tyr Gly 1285 Leu Met Ala 0 Asn Lys His Gln Gln Val 133 Leu Asp Arg 1350 Ser Ala Ser 1365 Ser Gln Asp 0 His His His Met Leu Lys 141 Leu Thr Ser 1430	Leu Leu Asp 1240 Thr Ala Leu 5 Met Leu Leu Asn Thr Thr 1290 Lys Ala Leu 1305 Gly Leu Thr 1320 Val Lys Phe 5 Tyr Gly Arg Ile Val Ser 1370 Leu Ser Gly 1385 Val Ile Cys 1400 Ile Ser Ser 5 Glu Glu Glu	I24 Ile Lys Ala 1260 Glu His Gly 1275 Leu His Tyr Leu Leu Tyr Pro Leu Leu 132 Leu Ile Lys 1340 Thr Ala Leu 1355 Leu Leu Leu Gln Thr Ala Gln Leu Leu 140 Glu Asn Ser 1420 Ser Gln Arg 1435 Gln Glu Pro	Gln Leu Asn  Val Gln Cys  Thr Asp Pro 128  Ala Ile Tyr 1295  Gly Ala Asp 1310  Leu Gly Val  5  Lys Lys Ala  Ile Leu Ala 136  Glu Gln Asn 1375  Arg Glu Tyr 1390  Ser Asp Tyr  5  Asn Pro Glu  Phe Lys Gly 144

120

1460 1465 1470 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly 1475 1480 1485 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu 1490 1495 1500 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys 1505 1510 1515 152 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser 1525 1530 1535 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu 1540 1545 1550 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser 1555 1560 1565 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe 1570 1575 1580 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe 1585 1590 1595 160 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly 1605 1610 1615 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro 1620 1625 1630Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln 1640 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile 1650 1655 1660 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser 1665 1670 1675 168 Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn 1685 1690 1695 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr 1700 1705 1710 Met Lys His Gln Ser Gln Leu 1715 <210> 379 <211> 656 <212> PRT <213> Homo sapien <400> 379 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys 1 5 10 15 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe 25 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp 40 45 35 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp 50 55 60

Lov	ui e	Leu	- ומ	50×	<b>Δ1</b> =	Den	Glu	Δος	Ser	G1	V=1	Va1	Lue	Len	ī.eu
			Ala 180				-	185					190		
	-	195	Arg	_			200					205			
	210		Lys			215	_				220	_			
Leu 225	Leu	Glu	His	Gly	Thr 230	Asp	Pro	Asn	Ile	Pro 235	Asp	Glu	Tyr	Gly	Asn 240
Thr	Thr	Leu	His	Tyr 245	Ala	Ile	Tyr	Asn	Glu 250	Asp	Lys	Leu	Met	Ala 255	Lys
Ala	Leu	Leu	Leu 260	Tyr	Gly	Ala	Asp	Ile 265	Glu	Ser	Lys	Asn	Lys 270	His	Gly
Leu	Thr	Pro 275	Leu	Leu	Leu	Gly	Val 280	His	Glu	Gln	Lys	Gln 285	Gln	Val	Val
Lys	Phe 290	Leu	Ile	Lys	Lys	Lys 295	Ala	Asn	Leu	Asn	Ala 300	Leu	Asp	Arg	Tyr
Gly 305	Arg	Thr	Ala	Leu	Ile 310	Leu	Ala	Val	Суз	Cys 315	Gly	Ser	Ala	Ser	Ile 320
			Leu	325					330					335	
			Thr 340					345					350		
Ile	Суѕ	Gln 355	Leu	Leu	Ser	Asp	Tyr 360	Lys	Glu	Lys	Gln	Met 365	Leu	Lys	Ile
Ser	Ser 370	Glu	Asn	Ser	Asn	Pro 375	Glu	Gln	Asp	Leu	Lys 380	Leu	Thr	Ser	Glu
Glu 385	Glu	Ser	Gln	Arg	Phe 390	Lys	Gly	Ser	Glu	Asn 395	Ser	Gln	Pro	Glu	Lys 400
			Glu	405					410					415	
·			Lys 420					425					430		
		435	Gly				440					445			
	450	_	Ser	_		455					460				
465			Tyr		470					475					480
			Pro	485					490					495	
	_		Thr 500					505					510		
Asn	Gly	Gln 515	Pro	Glu	Leu	Glu	Asn 520	Phe	Met	Ala	Ile	Glu 525	Glu	Met	Lys
Lys	530	_	Ser			535	_				540				_
Ala 545			Gly		550					555					560
			Glu	565					570					575	
		_	Glu 580			-		585	_			_	590		
		595	Ile				600					605			
	610		Val			615					620				
625		-	Asp		630					635					640
Ala	Met	Leu	Arg	Leu 645	Glu	Leu	Asp	Thr	Met 650	Lys	His	Gln	Ser	Gln 655	Leu

122

<211> 671 <212> PRT <213> Homo sapien

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123

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 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
                 485
                                     490
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
                                 505
                                                     510
             500
 Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp
                             520
                                                 525
 Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys
                         535
 His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala
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                    550
                                         555
 Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg
                                     570
                 565
                                                         575
 Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His.
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                                                     590
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 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn
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                                                 605
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile
                                             620
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 Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys
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 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala
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124

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<211> 155

<212> PRT

<213> Homo sapiens

<400> 383

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His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln 35 40

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe 50 60

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly 65 70 75 80

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala

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90
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Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
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Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
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gegacettgg cecgaagget etageaagga eccacegace ceageegegg eggeggegge 180
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ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacagg 300
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aagcctatgg ccagetgtet ttgtgtteee teteaceege etgteeteac agetgagaet 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
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naantingat niccanagee etacecaten tagitetget eteceaeegg niaceageee 240
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<221> misc_feature
<222> (1)...(277)
<223> n = A, T, C \text{ or } G
<400> 392
atattgttta acteetteet ttatatettt taacatttte atggngaaag gttcacatet 60
agteteactt nggenagngn etectacttg agtetettee eeggeetgnn eeagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
tqcaqtqcac caccctqtcc actacqtgat gctqtaggat taaaqtctca caqtgggcgg 240
ctgaggatac agcgccgcgt cctgtgttgc tggggaa
<210> 393
<211> 566
<212> DNA
<213> Homo sapiens
<400> 393
actagtccag tgtggtggaa ttcgcggccg cgtcgacgga caggtcagct gtctggctca 60
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacgtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
qaqaaqqtct aqtttqtcca tcaqcattat catqatatca ggactggtta cttggttaag 240
gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300
qqqtqqtttt caaaagtaga aatgteetgt atteegatga teateetgta aacattttat 360
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
cattetetee ctgagtttta atttttetee aaagttattt taatetatac aattaaaage 540
ttttgcctat caaaaaaaaa aaaaaa
<210> 394
<211> 384
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (384)
<223> n = A, T, C or G
<400> 394
quacatacat qtcccqqcac ctqaqctqca qtctqacatc atcqccatca cqgqcctcqc 60
tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
qcaqqaqqac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
teccaagatt ategggagaa agggggeagt aattaeecaa ateeggttgg ageatgaegt 240
```

```
qaacatccaq tttcctqata aggacgatgg gaaccagccc caggaccaaa ttaccatcac 300
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt
<210> 395
<211> 399
<212> DNA
<213> Homo sapiens
<400> 395
ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgac 60
totgacettg gactocaaga cotacatcaa cageetgget atattagatg atgagecagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
atteacgtet ttecagtace etgagttete tatagagttg cetaacacag geagaattgg 240 ceagetactt gtetgeaatt gtatetteaa gaataceetg geeateeett tgaetgaegt 300
caagttetet ttggaaagee tgggeatete eteactacag acetetgace atgggaeggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac
<210> 396
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (403)
<223> n = A,T,C or G
<400> 396
tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120 agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt
                                                                          403
<210> 397
<211> 100
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(100)
<223> n = A, T, C or G
actagincag tgtggtggaa ttcgcggccg cgtcgaccta naanccatci ctatagcaaa 60
tocatococg ctcctggttg gtnacagaat gactgacaaa
<210> 398
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(278)
<223> n = A, T, C or G
<400> 398
```

```
geggeeget egacageagt teegeeageg etegeeeetg ggtggggatg tgetgeaege 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180 ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg
<210> 399
<211> 298
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (298)
<223> n = A, T, C or G
acggaggtgg aggaagcgnc cctqqqatcg anaggatggg tcctgncatt gaccncctcn 60
ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180 ccggcattga gcgcatgggc ccgctgggcc tcgaccacat ggcctccanc attgancgca 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg
<210> 400
<211> 548
<212> DNA
<213> Homo sapiens
<400> 400
acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttcctgcctt 60
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaaggt 120
tgcagaggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300
tataccetet caccatecce ttgtetaete tgatgeecce aagatgeaac tgggeageta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccaqtq atctcctacc atqqqccccc ctcctqqqat caaqcccctc ccaqqccctq 480
tecceageee etectgeeee ageceaeeeg ettgeettgg tgeteageee teccattggg 540
agcaggtt
<210> 401
<211> 355
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A, T, C or G
<400> 401
actgtttcca tgttatgttt ctacacattg ctacctcagt gctcctggaa acttagcttt 60
tgatgtetee aagtagteea cetteattta actetttgaa actgtateat etttgeeaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctqtg qtcccttcca atqctgnqgg tttccaacca gqggaaqggt 300
cccttttqca ttqccaaqtq ccataaccat qaqcactact ctaccatqqn tctqc
<210> 402
<211> 407
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc_feature
<222> (1) ... (407)
<223> n = A, T, C or G
<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60
totoacatgo ggtggcatac ataggotoaa aataaaggaa tggagaaaaa tatttcaago 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggaget teteceetge agagagteee tgateteeea aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (303)
<223>.n = A,T,C or G
<400> 403
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcaccaaa 60
tectaageaa gageeatgge atggtgaaaa tgeaaaagga gagtetggee aatetacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tottaacaac gaccgaaacc cattatttac ataaacctcc attcggtaac catgttgaaa 300
gga
                                                                   303
<210> 404
<211> 225
<212> DNA
<213> Homo sapiens
aagtgtaact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
<210> 405
<211> 334
<212> DNA
<213> Homo sapiens
<221> misc_feature
<222> (1) ... (334)
<223> n = A, T, C or G
<400> 405
qaqctqttat actqtqaqtt ctactaqqaa atcatcaaat ctqaqqqttq tctqqaqqac 60
ttcaatacac ctccccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
cactetecae teteteanng tggateceae eect
                                                                   334
```

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<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A, T, C or G
<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
gaaacaaaca cccaataaac toggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant
                                                                   216
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
qtacaacatt qcacccaqtq tcaqattcta cacctqqcca ctcaqqaaqc aaqaqttaat 180
cccagaggte tatgtectaa tgtgttatgg caaatggatg teatgeaegt acctteattt 240
ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag
                                                                   413
<210> 408
<211> 183
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (183)
<223> n = A, T, C or G
<400> 408
ggagetngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tnettaacta gttaateett aaagggetan ntaateetta aetagteeet eeattgtgag 120
cattateett ecagtatten cettetnttt tatttactee tteetggeta eccatgtact 180
ntt
<210> 409
<211> 250
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(250)
<223> n = A, T, C or G
<400> 409
cccacgcatg ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gteectectt caacaacata ggaggateet eceettettt etgeteacgg cettatetag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
ggccntatgc
```

PCT/US00/27464

132

WO 01/25272

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<210> 410
<211> 306
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (306)
<223> n = A,T,C or G
<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60 agtcttgcaa tcccatttgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgctteet tetttattgc cccttettat ttatgtgaac 240
nactggttgg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(261)
<223> n = A, T, C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
qqatcttttq tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (231)
<223> n = A, T, C or G
```

PCT/US00/27464 WO 01/25272

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<400> 413
aactettaca atccaagtga etcatetgtg tgettgaate etttecaetg teteatetee 60 etcatecaag tttetagtae ettetetttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tecteatttg gaacetaaaa actetettet teetgggtet gagggeteea 180
agaatcottg aatcanttot cagatcattg gggacaccan atcaggaacc t
<210> 414
<211> 234
<212> DNA
<213> Homo sapiens
<400> 414
actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
gatggagetg aaaacataac ccactetgte etggaggeac tgggaageet agagaagget 120
gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180
ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca
<210> 415
<211> 217
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (217)
<223> n = A, T, C or G
<400> 415
gcataggatt aagactgagt atcttttcta cattcttta actttctaag gggcacttct 60
caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc
<210> 416
<211> 213
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (213)
<223> n = A, T, C or G
<400> 416
atgcatatnt aaagganact geetegettt tagaagacat etggnetget etetgeatga 60
ggcacagcag taaagctett tgatteecag aatcaagaac teteceette agactattae 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aag
<210> 417
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (303)
<223> n = A,T,C or G
<400> 417
nagtottoag goccatoagg gaagttoaca otggagagaa gtoatacata tgtactgtat 60
```

```
gtqqqaaagg ctttactctg aqttcaaatc ttcaagccca tcagagagtc cacactggag 120
 agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180 ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
 tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
                                                                      303
 <210> 418
 <211> 328
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1) ... (328)
 <223> n = A,T,C or G
 tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
 tgcacaggea tgatetegge teactacaac ecetgeetee catgtecaag egattettgt 120
 gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagttttt 180
 gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
 tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300
 aaagtgctan gattacaggc cgtgagcc
 <210> 419
 <211> 389
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1) ... (389)
 <223> n = A, T, C or G
 <400> 419
 cetecteaag aeggeetgtg gteegeetee eggeaaceaa gaageetgea gtgeeatatg 60
 accectgage catggactgg agectgaaag geagegtaca ecetgeteet gatettgetg 120
 cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180
 cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt gtgccaggca 240
 ceggttetec agecaceaac etcacteget eeegcaaatg geacateagt tettetacee 300
 taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg
                                                                      389
 <210> 420
 <211> 408
 <212> DNA
 <213> Homo sapiens
 <400> 420
 gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
 tggccagggc agcaagcctt agccttggct tettgtttet getttttte tggctagace 120
 gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
 gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
 gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
 gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt egaageacag 360
 acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg
 <210> 421
 <211> 352
 <212> DNA
 <213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1) ... (352)
<223> n = A, T, C or G
<400> 421
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
qaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagaticttt ggcagitgtc tttgtcataa cccacaggtg tagaaacaag 240
qqtqcaacat qaaatttctq tttcqtagca agtgcatgtc tcacaagttq gcangtctgc 300
cactecgagt ttattgggtg tttgttteet ttgagateca tgeattteet gg
<210> 422
<211> 337
<212> DNA
<213> Homo sapiens
<400> 422
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gegatageaa ggtgeeggeg ategeggegg egteaateet ggeeaaggte ageegtgate 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gettetteeg eeggtaegge tggeetatga aaattat
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A, T, C or G
<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
teactgacag aacaggtett ttttgggtee ttetteteea ecaegatata ettgeagtee 180
teettettga agattetttg geagttgtet ttgteataac ceacaggtgt anaaacaagg 240
gtgcaacatg aaatttetgt ttegtageaa gtgcatgtet cacagttgte aagtetgeee 300
tccgagttta
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A,T,C or G
<400> 424
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120 cactgacaga acaggtcttt tttgggtcct tcttctccac cacgatatac ttgcagtcct 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240
agttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
tccqtcgacg
```

```
<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (216)
<223> n = A, T, C or G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
anattatcca ttatnttaag ggttgacttc aggntacagc acacagacaa acatgcccag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
                                                                   216
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420 ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(107)
<223> n = A, T, C or G
<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
<210> 428
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (38)
<223> n = A, T, C or G
gaacttccna anaangactt tattcactat tttacatt
                                                                   38
<210> 429
```

137

```
<211> 544
<212> DNA
<213> Homo sapiens
<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagage ggctgcagce ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actottgaag gactttctga tttatccaca atcaaatcat cggttttcag 180 tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
quettecact teagttacae etcacteace atceteteet griggitetg tgetgettea 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ticagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(507)
<223> n = A, T, C or G
<400> 430
cttateneaa tqqqqetece aaacttqqet qtqcaqtqqa aacteeqqqq qaattttqaa 60
gaacactgac acccatcttc caccccgaca ctctgattta attgggctgc agtgagaaca 120
gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caaqaaqqaq qactqcaaqt atatcqtqqt qgaqaaqaaq gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaagat 480
ttttgagcaa aaaaaaaaa aaaaaaa
<210> 431
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
<223> n = A,T,C or G
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
gcaatgagtc tggcttttac tctgctgttt ct
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
```

<220>

```
<221> misc feature
<222> (1) ... (387)
<223> n = A, T, C or G
<400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
aaatgcaagg caacatgtgt agatctcttg tettattett ttgtetataa tactgtattg 120
ngtagtecaa geteteggna gtecagecae tgngaaacat getecettta gattaacete 180 gtggaenetn ttgttgnatt gtetgaactg tagngeeetg tattttgett etgtetgnga 240
attictgttgc ttictggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctgaattq ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
acaacgtata gaacactgga gtccttt
<210> 433
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (281)
<223> n = A, T, C or G
<400> 433
ttcaactage anagaanact getteagggn gtgtaaaatg aaaggettee aegeagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggenetat ttgggttgge tggaggaget gtggaaaaca tggagagatt ggegetggag 180
ategeogtgg ctattecten ttgntattac accagngagg ntetetgtnt geceactggt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t
<210> 434
<211> 484
<212> DNA
<213> Homo sapiens
<400> 434
ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60
aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
tqttqcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
agctagtcta tcagcatctg acaggtgaat tggatggttc tcagaaccat ttcacccaga 300
cagcotgttt ctatcotgtt taataaatta gtttgggttc totacatgca taacaaaccc 360
toctccaatc totcacataa aagtetotoa ettoaagttt agteageacc cecaccaaac 420
titatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
ttta
<210> 435
<211> 424
<212> DNA
<213> Homo sapiens
<400> 435
gegeegetea gageaggtea etttetgeet tecaegteet eetteaagga ageeeeatgt 60
gggtagettt caatategea ggttettaet eetetgeete tataagetea aacceaceaa 120
cqatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420
aaac
```

<210> 436

```
<211> 667 .
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(667)
<223> n = A, T, C or G
<400> 436
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tectggeeat gtaateetga aagtttteee aaggtageta taaaateett ataagggtge 120
agcetettet ggaatteete tgattteaaa gteteaetet caagttettg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
qccaqqtttq tcataqcact catcaaagtc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agtteataat getgeteeat geceagetgg gtgagttgge caaateettg tggeeatgag 480
gatteettta tggggteagt gggaaaggtg teaatgggae tteggtetee atgeegaaac 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag
<210> 437
<211> 693
<212> DNA
<213> Homo sapiens
<400> 437
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaact tcagacagct ttttcagatc 180
ataaaaqata attettagee catgttette tecagageag acetgaaatg acagcacage 240
aggtactect ctattttcac cectettqct tetactetet qqcaqtcaqa cetqtgggag 300
gccatgggag aaagcagcte tetggatgtt tgtacagate atggactatt etetgtggae 360
cattteteca ggttacceta ggtgteacta ttggggggac agecageate tttagettte 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg tigetteaga gatgietgia actatetggg ggetetgitg getetttace 660
ctgcatcatg tgctctcttg gctgaaaatg acc
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
```

PCT/US00/27464

```
<222> (1)...(431)
<223> n = A, T, C or G
<400> 439
gttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gcttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
qtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
qccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cgaagcacag 360
acqttgaccq gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t
<210> 440
<211> 523
<212> DNA
<213> Homo sapiens
<400> 440
agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatettttg tatttaagga tietgagatt tigettgage aggattagat aaggetgite 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta
<210> 441
<211> 430
<212> DNA
<213> Homo sapiens
<400> 441
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag tigaagtitg tgacittggt gittcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt egaageacag 360
acqttqaccq gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
                                                                   430
aatttagtag
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctggaa tgacaattat attttaactt tggtggggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1)...(624)
<223> n = A, T, C or G
<400> 443
tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60
ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180
tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360
taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420
atggtaaaca teettattat taaagteaac getaaaatga atgtgtgtge atatgetaat 480
agtacagaga gagggcactt aaaccaacta agggcctgga gggaaggttt cctggaaaga 540
ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600
ttgtccctat ctgctaaaca gatc
<210> 444
<211> 425
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (425)
<223> n = A, T, C or G
<400> 444
gcacatcatt nntcttgcat tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
gaagetttgt ccaggeetgt gtgtgaacce aatgttttge ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcatcctgt gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga
                                                                   425
<210> 445
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (414)
<223> n = A, T, C or G
catgtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120
tgaaattett tgeatgtgge agattattgg atgtagttte etttaactag catataaate 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatcctactc acaaatgact aggcttctcc tcttgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag
<210> 446
<211> 631
<212> DNA
<213> Homo sapiens
```

142

<220> <221> misc\_feature <222> (1)...(631) <223> n = A, T, C or G<400> 446 acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60 tetgeatgea tgggaagtgt gageatteta teaatatgea ggageeatet tgeaggtgtg 120 atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180 ccqqtcctqt acqatttcaq tatqtcttaa tcgcagctgt gattggaaca attcagattg 240 ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300 actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360 gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tecacgaggt 420 taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480 caqtattata qacaaaaqaa taaqacaaga gatctacaca tgttgccttg catttgtggt 540 aatctacacc aatgaaaaca tgtactacag ctatatttga ttatgtatgg atatatttga 600 aatagtatac attgtcttga tgttttttct g <210> 447 <211> 585 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1) ... (585) <223> n = A, T, C or G<400> 447 ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60 cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120 quetettetq quatteetet quetteaaag teteaetete aagttettga aaacgaggge 180 agttcctgaa aggcaggtat agcaactgat cttcagaaag aggaactgtg tgcaccggga 240 tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300 ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360 gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420 gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480 attectttat ggggteagtg ggaaaggtgt caatgggact teggteteca tgeegaaaca 540 ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta <210> 448 <211> 93 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1)...(93) <223> n = A,T,C or G<400> 448 tgctcgtggg tcattctgan nnccgaactg accntgccag ccctgccgan gggccnccat 60 ggctccctag tgccctggag agganggggc tag <210> 449 <211> 706 <212> DNA <213> Homo sapiens

<220>

<221> misc\_feature

```
<222> (1)...(706)
<223> n = A, T, C or G
ccaaqttcat gctntgtgct ggacgctgga cagggggcaa aagcnnttgc tcgtgggtca 60
ttetganeae egaactgace atgeeageee tgeegatggt cetecatgge teectagtge 120
cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180 cggggacagc atcctgcaga tggtcgggcg cgtcccattc gccattcagg ctgcgcaact 240
qttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300
gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcncga cgttgtaaaa 360
cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcatgcacg 420
cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480
cgacqtggga tecneactga gagagtggag agtgacatgt getggaenet gtecatgaag 540
cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600
aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660
706
<210> 450
<211> 493
<212> DNA
<213> Homo sapiens
<400> 450
qaqacqqaqt qtcactctqt tgcccaggct ggaqtqcagc aagacactqt ctaagaaaaa 60
acagttttaa aaggtaaaac aacataaaaa gaaatatcct atagtggaaa taagagagtc 120
aaatgaggct gagaacttta caaagggatc ttacagacat gtcgccaata tcactgcatg 180
agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
caagtcaggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300
agagacactg tcagagagtt aaaaagtgag ttctatccat gaggtgattc cacagtcttc 360
tcaagtcaac acatctgtga actcacagac caagttetta aaccactgtt caaactctgc 420
tacacatcag aatcacctgg agagetttac aaactcccat tgccgagggt cgacgcggcc 480
gcgaatttag tag
<210> 451
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (501)
<223> n = A, T, C or G
<400> 451
gggcgcgtcc cattcgccat tcaggctgcg caactgttgg gaagggcgat cggtgcgggc 60
ctettegeta ttacgecage tggegaaagg gggatgtget gcaaggegat taagttgggt 120 aacgecaggg tttteccagt enegacgttg taaaacgaeg gecagtgaat tgaatttagg 180
tgacnetata gaagagetat gaegtegeat geaegegtae gtaagettgg atcetetaga 240
acqueeqcet actactacta aattegegge egegtegacg tgggateene actgagagag 300
tggagagtga catgtgctgg acnotgtoca tgaagcactg agcagaagct ggaggcacaa 360
cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420
gttqcaatqa qctqaqatca qqccnctqcn ccccaqcatq qatqacaqaq tqaaactcca 480
tcttaaaaaa aaaaaaaaaa a
                                                                      501
<210> 452
<211> 51
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(51)
```

```
<223> n = A, T, C or G
<400> 452
agacggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c
                                                                             51
<211> 317
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Val Ser Ile Trp Asn Pro Ile Leu Leu Trp Gln Pro Ile Pro Val His

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705 710 715 720 Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val 870 Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys 985 Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp Ser Ala 1015 Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser Ile Val 1030

158

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## (19) World Intellectual Property Organization International Bureau



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#### (43) International Publication Date 12 April 2001 (12.04.2001)

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- (25) Filing Language:

English

(26) Publication Language:

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4 October 1999 (04.10.1999) US

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- (72) Inventors; and
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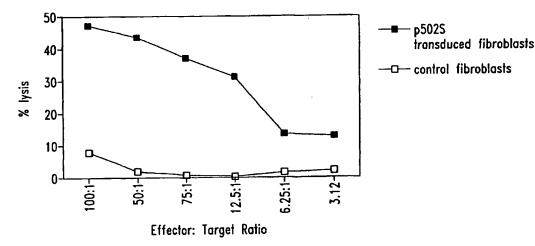
- (74) Agents: POTTER, Jane, E., R. et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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#### Published:

- with international search report
- (88) Date of publication of the international search report: 20 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.

75777 A3

Inti Vional Application No PCT/US 00/27464

A. CLASSIFICATION OF SUBJECT MATTER
1PC 7 C12N15/12 C12N15/62 C07K16/30 C1201/68 C07K14/47 A61K39/00 A61K39/395 A61P35/00 G01N33/547 G01N33/68 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED  $\frac{\text{Minimum documentation searched (classification system followed by classification symbols)}{IPC~7~~C12N~~C07K~~C12Q~~G01N~~A61K~~A61P}$ Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category ' 1-15. WO 98 37093 A (CORIXA CORPORATION) Χ 17-19, 27 August 1998 (1998-08-27) 21,22, 29-31, 34,35, 39-42, 44-46, 48,49, 53-55, 58-79 see especially SEQ ID NOS: 2, 3, 107 and the whole document -/--Patent family members are listed in annex. Further documents are listed in the continuation of box C. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international filing date "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "O" document referring to an oral disclosure, use, exhibition or "P" document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 2 4 APR 2001 19 January 2001 Authorized officer Name and mailing address of the ISA European Patent Office. P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016 Fuchs, U

Intr tional Application No
PC I'/US 00/27464

		PC1/US 00/2/464
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х	WO 98 37418 A (CORIXA CORPORATION) 27 August 1998 (1998-08-27)	1-15, 17-19, 21,22, 29-31, 34,35, 39-42, 44-46, 48,49, 53-55, 58-79
	see especially SEQ ID NOS: 2, 3, 107 and 108 the whole document	
x	EMBL database, Heidelberg, FRG Emhum1 accession number AF047020 20 February 1998 ALBERS, C. ET AL.: "Homo sapiens alpha-methylacyl-CoA racemase mRNA, complete cds." XP002157763 the whole document -& EMBL database, Heidelberg, FRG Trembl accession number 043673 01 June 1998 ALBERS, C. ET AL.: "ALPHA-METHYLACYL-COA RACEMASE (EC 5.1.99.4)" XP002157764 the whole document	1,4,5,7-12
P,X	WO 00 04149 A (CORIXA CORPORATION) 27 January 2000 (2000-01-27) see especially SEQ ID NOS: 2, 3, 107 and 108 the whole document	1-79
A	US 5 925 362 A (SPITLER, L.E. ET AL.) 20 July 1999 (1999-07-20)	35, 39-49, 53-57
А	the whole document  SJÖGREN, H.O.: "Therapeutic immunization against cancer antigens using gentically engineered cells" IMMUNOTECHNOLOGY, vol. 3, no. 3, October 1997 (1997-10), pages 161-172, XP004097000 the whole document	23-28, 32-34, 53-57

Intr tional Application No
PUÍ/US 00/27464

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Delevent to dain \$1-
ategory *	Citation of document, with indication, where appropriate, of the relevant passages  •	Relevant to daim No.
1	CHU, R.S. ET AL.: "CpG Oligodeoxynucleotides Act as Adjuvants that Switch on T Helper 1 (Th1) Immunity" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 186, no. 10, 17 November 1997 (1997-11-17), pages 1623-1631, XP002910130 the whole document	14-16, 18-20, 25-27, 41-43, 45-47
١	EP 0 317 141 A (BECTON DICKINSON AND COMPANY) 24 May 1989 (1989-05-24) the whole document	50-52
<u>.</u> .		
•		

PCT/US 00/27464

### INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 29-34, 48, 49, 52 and 55-57 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-79 PARTIALLY
Remark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-79 partially

Invention 1

An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein as defined by the SEQ ID NO: 108 (corresponding to clone F1-12), wherein said polypeptide being encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 2, 3 and 107 (each corresponding to clone F1-12), fragments or variants of said polypeptide, fusion proteins comprising said polypeptide, polynucleotides or oligonucleotides derived from said polynucleotides, antibodies or fragments thereof binding to said polypeptide, pharmaceutical compositions or vaccines comprising said products and their use in methods for inhibiting, monitoring or diagnosing the development of a prostate cancer, for removing tumor cells from a a sample or for expanding and / or stimulating T-cells:

2. Claims: 1-79 partially

Invention 2

Idem as subject 1 but limited to the clone J1-17 (SEQ ID NOS: 8, 9, 109 and 112);

3.-445. Claims: 1-79 partially (as far as applicable)

Inventions 3-445

Idem as subject 1 but limited to SEQ ID NOS: 1, 4-7, 10-106, 110, 111, 113-305, 307-315, 326-335, 339-375 and 381-472.

information on patent family members

Intr Ional Application No PCI/US 00/27464

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